Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
August 10, 2022

Table of Contents

Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document
P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to ensure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved.

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are preferred with clinical criteria, are non-preferred status, or if they required PA prior to the PDL.

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Accumulation Edit
Brand Limit Switchover
Dispense As Written Override
Early Refill
Ingredient Duplication
Maintenance Supply Opt Out
Maximum Unit/Max Cost Limitations
Short Acting Opioid Naïve Override
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-10 code(s) may be used. Use of ICD-10 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Respiratory Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- For a diagnosis of allergic rhinitis, the patient must also have failed 30-day treatment trials with at least two prescribed antiallergic agents, to include oral antihistamines or intranasal corticosteroids either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- For all other diagnoses, the patient must also have failed 30-day treatment trials with at least two prescribed and preferred respiratory agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- Requests for Pulmicort Respules® or Singulair® will not require failed therapy for children under age five with a diagnosis of asthma.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Respiratory agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Intranasal Corticosteroids

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred intranasal corticosteroids in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Intranasal corticosteroid agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Antiallergic Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- For ophthalmic products, the patient must also have failed 14-day treatment trials with at least two prescribed and preferred ophthalmic agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- For nasal products, the patient must have also failed 14-day treatment trials with at least two prescribed antiallergic agents, to include oral antihistamines, intranasal corticosteroids or intranasal cromolyn, either generic, OTC or brand within the past 6 months or have a documented allergy or contraindication to all preferred or acceptable agents.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- EENT antiallergic agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Antibacterial Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 3-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 30 days or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Not Applicable

Verbal PA Requests

PA requests that meet prior usage requirement for approval may be accepted verbally.

EENT Vasoconstrictor Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 3-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- EENT vasoconstrictors are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Complement Inhibitors for the Treatment of Hereditary Angioedema

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must have documentation of >1 severe event per month despite treatment trials with an antifibrinolytic agent (e.g., aminocaproic acid or tranexamic acid) AND an attenuated androgen (e.g., danazol, oxandrolone, oxymetholone, or methyltestosterone), unless there is a documented adverse response or contraindication to the use of these agents.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Hereditary angioedema agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

August 10, 2022
1:00 p.m. – 3:00 p.m.

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1. Opening remarks……...……. Chair
2. Approval of May 4, 2022 P&T Committee Meeting minutes……...……..……...Chair
3. Pharmacy program update……Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives
   (prior to each respective class review)
5. Pharmacotherapy class re-review….University of Massachusetts Clinical Pharmacy Services
   - Inhaled Antimuscarinics – AHFS 120808
   - Respiratory β-adrenergic agonists – AHFS 121208
   - Leukotriene Modifiers – AHFS 481024
   - Inhaled Mast-cell Stabilizers – AHFS 481032
   - Respiratory Agents-Corticosteroids – AHFS 481008
   - Respiratory Smooth Muscle Relaxants – AHFS 861600
   - Intranasal Corticosteroids – AHFS 520808
   - Eye, Ear, Nose and Throat Preparations-Antiallergic Agents – AHFS 520200
   - Eye, Ear, Nose and Throat Preparations -Antibacterials – AHFS 520404
   - Eye, Ear, Nose and Throat Preparations -Vasoconstrictors – AHFS 523200
   - Androgens – AHFS 680800
   - Complement Inhibitors for HAE – AHFS 923208
   - Growth Hormone Agents - AHFS 682800
6. Results of voting announced……...Chair
7. New business
8. Next meeting date
   - November 9, 2022
   - February 8, 2023
   - May 3, 2023
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Antimuscarinics
AHFS Class 120808
August 10, 2022

I. Overview

The inhaled antimuscarinics are approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-10] Tiotropium is also approved to reduce exacerbations in patients with COPD and for the maintenance treatment of asthma (Respimat® formulation only).[7-8,11] These agents antagonize the action of acetylcholine at its receptor site and produce bronchodilation by inhibiting cholinergic receptors in bronchial smooth muscle. The effect is site-specific and leads to dilation of both large and small airways.[1-10]

The inhaled antimuscarinics have been shown to alleviate dyspnea, improve exercise tolerance, decrease hyperinflation associated with COPD, and reduce the frequency of disease exacerbations. Tiotropium has a longer duration of action than ipratropium and can be dosed once daily.[2] Aclidinium was Food and Drug Administration (FDA)-approved in July 2012. Similar to tiotropium, aclidinium is a long-acting inhaled antimuscarinic but requires twice daily dosing.[3] Approved in April 2014, umeclidinium is also a long-acting agent approved for once-daily use.[9] Lonhala Magnair® is a formulation of glycopyrrolate that is dosed twice-daily via nebulizer.[4] Yupelri® (revefenacin) was FDA-approved in November 2018 for the maintenance treatment of patients with COPD. It is administered once daily via nebulizer.[6]

The inhaled antimuscarinics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ipratropium inhalation solution is the only product that is available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Inhaled Antimuscarinics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aclidinium	dry powder inhaler	Tudorza Pressair®	Tudorza Pressair®
Glycopyrrolate	inhalation solution	Lonhala Magnair®	none
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	ipratropium, Atrovent HFA®
Revefenacin	inhalation solution	Yupelri®	none
Tiotropium	dry powder inhaler, solution inhaler	Spiriva Handihaler®, Spiriva Respimat®	Spiriva Handihaler®, Spiriva Respimat®
Umeclidinium	dry powder inhaler	Incruse Ellipta®	Incruse Ellipta®

*Generic is available in at least one dosage form or strength.
HFA=hydrofluoroalkane, PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the inhaled antimuscarinics are summarized in Table 2.

Table 2. Treatment Guidelines Using the Inhaled Antimuscarinics

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive**	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, sputum production, history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease. • Spirometry is required to make the diagnosis; the presence of a post-bronchodilator Forced Expiratory Volume in one second (FEV_1)/ Forced Vital Capacity (FVC) ratio of <0.07 confirms the presence of persistent airflow

Clinical Guidelines	Recommendations
Pulmonary Disease (2022)[12]	limitation. • The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbation, hospital admissions, or death), in order to guide therapy. • Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer; these comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalizations independently. Prevention and maintenance therapy • Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. • The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present. • Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. • Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices. • Inhaler technique needs to be assessed regularly. • COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations. • Influenza vaccination decreases lower respiratory tract infections. • Pneumococcal vaccination decreases lower respiratory tract infections. • CDC recommends the Tdap vaccination (dTaP/dTPa) in COPD patients to protect against pertussis, tetanus and diphtheria, in those who were not vaccinated in adolescence and Zoster vaccine to protect against shingles for adults with COPD aged ≥50 years. • Pulmonary rehabilitation improves exercise capacity, symptoms and quality of life across all grades of COPD severity. • In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival. • In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. Individual patient factors must be considered when evaluating the patient's need for supplemental oxygen. • In patients with severe chronic hypercapnia and a history of hospitalizations for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization. • In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial. • Palliative approached are effective in controlling symptoms in advanced COPD. Pharmacologic therapy for stable COPD • Bronchodilators o Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. o Regular and as-needed use of short-acting β_2-agonist (SABA) or short-acting antimuscarinic (SAMA) improves FEV_1 and symptoms. o Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms. o Long-acting β_2-agonists (LABAs) and long-acting antimuscarinic agents

Clinical Guidelines	Recommendations
	(LAMAs) improve lung function, dyspnea, health status, and reduce exacerbation rates. o LAMAs have a greater effect on reducing exacerbations than LABAs and decrease hospitalizations. o Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy. o Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy. o Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance. o Theophylline exerts a small bronchodilator effect in stable COPD and that is associated with modest symptomatic benefits. • Anti-inflammatory therapy o Inhaled corticosteroids ▪ An inhaled corticosteroid (ICS) combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. ▪ Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease. ▪ Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations. o Oral glucocorticoids ▪ Long-term use of oral glucocorticoids has numerous side effects with no evidence of benefits. o Phosphodiesterase-4 (PDE4) inhibitors ▪ In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations, a PDE4 inhibitor improves lung function and reduces moderate to severe exacerbations and improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations. o Antibiotics ▪ Long-term azithromycin and erythromycin therapy reduces exacerbations over one year. ▪ Treatment with azithromycin is associated with an increased incidence of bacterial resistance and hearing test impairments. o Mucoregulators and antioxidant agents ▪ Regular treatment with mucolytics such as erdosteine, carbocysteine, and N-acetylcysteine (NAC) reduces the risk of exacerbations in select populations. o Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy. o Leukotriene modifiers have not been adequately tested in COPD patients. o Intravenous augmentation therapy may slow down the progression of emphysema. o There is no conclusive evidence of a beneficial role of antitussives in patients with COPD. Vasodilators do not improve outcomes and may worsen oxygenation. <u>Management of stable COPD</u> • LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea and for immediate relief of symptoms in patients

Clinical Guidelines	Recommendations
	already on long-acting bronchodilators for maintenance therapy. • Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. • Inhaled bronchodilators are recommended over oral bronchodilators. • Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable. • Long-term monotherapy with ICS is not recommended. • Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators. • Long-term therapy with oral corticosteroids is not recommended. • In patients with severe to very severe airflow limitation, chronic bronchitis, and exacerbations the addition of a PDE4 inhibitor to a treatment with long-acting bronchodilators with/without ICS can be considered. • Preferentially but not only in former smokers with exacerbations despite appropriate therapy, macrolides (in particular azithromycin) can be considered. • Statin therapy is not recommended for prevention of exacerbations. • Antioxidant mucolytics are recommended only in select patients. • Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. • Antitussives cannot be recommended. • Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD. • Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease. <u>Management of exacerbations</u> • The most common causes of an exacerbation are viral respiratory tract infections. • The goal of treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events. • SABA with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation. • Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge. • Systemic corticosteroids can improve lung function (FEV_1), oxygenation, and shorten recovery time and length of hospital stay. Duration of therapy should not be more than five to seven days. • Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be five to seven days. • Methylxanthines are not recommended due to increased side effect profiles.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice**	<u>Diagnosis</u> • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. <u>Treatment</u> • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted,

Clinical Guidelines	Recommendations
Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)[13]	treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
Department of Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2021)**[14]	Diagnosis and classification • Post-bronchodilator spirometry is suggested to confirm clinical diagnosis of COPD. • There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD. Risk reduction and first-line therapy • Smoking cessation is recommended for prevention and risk reduction of COPD. • Routine vaccination for influenza and pneumococcal pneumonia is suggested for prevention and risk reduction of COPD exacerbations. • LAMA is recommended as first-line therapy in patients with symptomatic COPD. • Inhaled LABA should not be offered as first-line therapy in patients with symptomatic COPD, unless a LAMA is not tolerated or is contraindicated. • ICS should not be offered to patients with symptomatic COPD as a first-line therapy. • For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a LAMA, adding a LABA to LAMA therapy is suggested. • If choosing dual therapy, offering LABA with ICS for patients with COPD is not recommended. • In patients with COPD who are on combination therapy with a LAMA/LABA and continue to have COPD exacerbations, adding an ICS as a third medication is suggested.

Clinical Guidelines	Recommendations
	• There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy. • Consider withdrawal of ICS in patients with COPD without moderate to severe exacerbations in the last two years. • There is insufficient evidence to recommend for or against the use of NAC preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). • There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not). • Providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia or chronic stable resting moderate hypoxemia with signs of tissue hypoxia is recommended. • Routinely offering ambulatory long-term supplemental oxygen is not suggested for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. • In patients with COPD, starting or continuing cardio-selective beta-blockers is suggested only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction). • Supported self-management program and telehealth support should be offered.

Global Initiative for Asthma:
Global Strategy for Asthma Management and Prevention (2021)[15]
	<u>General principles of asthma management</u>
	• The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.
	• Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers.
	• Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.
	• Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences.
	• For population-level decisions about asthma treatment, the 'preferred option' represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	<u>Medications and strategies for symptom control and risk reduction</u>
	• For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone.
	• This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms.
	• Choice of reliever
	  ○ Low dose ICS-formoterol is the preferred approach recommended by this guideline.
	  ○ SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy.
	• Mild asthma

Clinical Guidelines	Recommendations
	○ Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death. ○ In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. • Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique ○ Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities. ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium. ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age. ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA. ▪ For children, try other controller options at the same step before stepping up. ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. • Stepping down to find the minimum effective dose ○ Consider step down once good asthma control has been achieved and maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. • For all patients with asthma ○ Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect. ○ Encourage adherence with controller medication, even when symptoms are infrequent. ○ Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations. ○ For patients with one or more risk factors for exacerbations: ▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function). ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies). • Difficult-to-treat and severe asthma ○ Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on

Clinical Guidelines	Recommendations

therapy including biologics.

Categories of asthma medications

- *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise.
- *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
- *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.

Initial controller treatment

- For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.

Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age

- Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)					
Controller and preferred reliever (Track 1)	**Steps 1 to 2** As-needed low dose ICS-formoterol		**Step 3** Low dose maintenance ICS-formoterol	**Step 4** Medium dose maintenance ICS-formoterol	**Step 5** Add-on LAMA Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
	Reliever: as-needed low-dose ICS-formoterol				
Controller and	**Step 1** Take ICS	**Step 2** Low dose	**Step 3** Low dose	**Step 4** Medium/	**Step 5** Add-on LAMA

Clinical Guidelines	Recommendations

alternative reliever (Track 2)	whenever SABA taken	maintenance ICS	maintenance ICS-LABA	high dose maintenance ICS-LABA	Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
	Reliever: as-needed SABA				

- Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

Personalized management to control symptoms and minimize future risk (six to 11 years of age)					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller	Low dose ICS taken when SABA is taken	Daily low dose ICS	Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy	Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy. Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)
Other controller options	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken	Low dose ICS+LTRA	Add tiotropium, or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side effects
Reliever	As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)				

<u>Management of worsening asthma and exacerbations</u>

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak expiratory flow.
- For patients presenting with an exacerbation to a primary care or acute care facility:
  - Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy.
  - Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given.
  - Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be

Clinical Guidelines	Recommendations

reviewed after one hour.
- Ipratropium bromide treatment is recommended only for severe exacerbations.
- Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment.
- Chest X-ray or prescribing antibiotics is not routinely recommended.
- Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
- Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use.

- Arrange early follow-up after any exacerbation, regardless of where it was managed.
  - Review the patient's symptom control and risk factors for further exacerbations.
  - Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks.
  - Provide a written asthma action plan and advice about avoiding exacerbation triggers.
  - Check inhaler technique and adherence.

<u>Children five years and younger: assessment and management</u>

- The goals of asthma management in young children are similar to those in older patients:
  - To achieve good control of symptoms and maintain normal activity levels.
  - To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects.
- Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective.
- A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Personalized management of asthma in children 5 years and younger

	Step 1	Step 2	Step 3	Step 4
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td rowspan="2">Consider this step for children with:</td><td rowspan="2">Infrequent viral wheezing and no or few interval symptoms</td><td>Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year</td><td>Asthma diagnosis, and not well-controlled on low dose ICS</td><td>Not controlled on double ICS</td></tr>
<tr><td>Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months</td><td colspan="2">First check diagnosis, inhaler skills, adherence, exposures</td></tr>
</table>

<u>Management of worsening asthma and exacerbations in children five and younger</u>
• Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
• Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  ○ Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  ○ Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  ○ Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  ○ There is no compelling evidence to support parent-initiated OCS.
• In children presenting to primary care or an acute care facility with an asthma exacerbation:
  ○ Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%).
  ○ Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  ○ Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days for children attending an emergency department or admitted to hospital, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone.
  ○ Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma management.
</td></tr>
<tr><td>British Thoracic Society/ Scottish Intercollegiate Guidelines Network: British Guideline on the Management of Asthma (2019)[16]</td><td>
<u>Pharmacological management</u>
• The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication.
• Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.
• Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors.
• Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%.
</td></tr>
</table>

Clinical Guidelines	Recommendations
	• Intermittent reliever therapy: o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. o For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. o Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years of age with asthma. o ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: o In adults, the first choice add-on therapy to an ICS is a LABA, which should be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. o In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: o If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: o All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. o If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed)

Clinical Guidelines	Recommendations
	▪ Add tiotropium (adults) ▪ Add a theophylline. o If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). o Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored. o Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. o Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. o The use of immunotherapy is not recommended for the treatment of asthma in adults or children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the inhaled antimuscarinics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Inhaled Antimuscarinics[1-10]

Indication	Aclidinium	Glycopyrrolate	Ipratropium	Revefenacin	Tiotropium	Umeclidinium
Maintenance treatment of airflow obstruction associated with COPD, including chronic bronchitis and emphysema		✔				
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema			✔		✔	
Maintenance treatment of patients with COPD	✔			✔		✔
Reduce exacerbations in COPD patients					✔	
Maintenance treatment of asthma					✔ *	

COPD=chronic obstructive pulmonary disease.
*Respimat® formulation only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the inhaled antimuscarinics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Inhaled Antimuscarinics[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aclidinium	6	Not reported	Not reported	Feces (20 to 33) Renal (0.09)	5 to 8
Glycopyrrolate	40	38 to 41	Liver	Renal (60 to 85) Bile (<5)	33 to 53
Ipratropium	<1 to 7	Not reported	Liver	Feces (48) Renal (2.8)	2.0 to 3.8
Revefenacin	<3	71	Liver	Feces (88) Renal (<1)	22 to 70
Tiotropium	20 (dry powder) 33 (solution)	72	Liver (25)	Renal (12 to 19) Feces (% not reported)	120 to 144 (dry powder) 25 to 44 (solution)
Umeclidinium	Not reported	89	Not reported	Renal (<1) Feces (92)	11

V. Drug Interactions

Major drug interactions with the inhaled antimuscarinics are listed in Table 5.

Table 5. Significant Drug Interactions with the Inhaled Antimuscarinics[2]

Generic Name(s)	Interaction	Mechanism
Aclidinium, glycopyrrolate, ipratropium, revefenacin, tiotropium, umeclidinium	Anticholinergics	Concurrent use of inhaled antimuscarinics and anticholinergics may result in increased risk of anticholinergic side effects.
Aclidinium, glycopyrrolate, tiotropium, umeclidinium	Bupropion	Concurrent use of bupropion and inhaled antimuscarinics may result in lower seizure threshold.
Aclidinium, glycopyrrolate, tiotropium. umeclidinium	Donepezil	Concurrent use of donepezil and inhaled antimuscarinics may result in reduced seizure threshold.
Revefenacin	OATP1B1/1B3 Inhibitors (rifampin, gemfibrozil, cyclosporine, eltrombopag)	Concurrent use of revefenacin and OATP1B1/1B3 inhibitors may result in increased exposure of the active metabolite of revefenacin.

VI. Adverse Drug Events

The most common adverse drug events reported with the inhaled antimuscarinics are listed in Table 6. In January 2010, the Food and Drug Administration (FDA) issued a follow-up to the previous early communication (October 2008), which described a potential increase in the risk of stroke, heart attack, or death from a cardiovascular cause related to the use of tiotropium.[17] The FDA completed its review and believes the available data do not support an association between the use of tiotropium and an increased risk for these serious adverse events.[18]

Table 6. Adverse Drug Events (%) Reported with the Inhaled Antimuscarinics[1-10]

Adverse Events	Aclidinium	Glycopyrrolate	Ipratropium	Revefenacin	Tiotropium	Umeclidinium
Cardiovascular						
Arrhythmia	-	<1	<1	-	<1	<1

Adverse Events	Aclidinium	Glycopyrrolate	Ipratropium	Revefenacin	Tiotropium	Umeclidinium
Chest pain	-	-	3	-	1 to 7	-
Edema	-	-	-	-	5	-
Hypotension	-	-	<1	-	-	-
Palpitation	-	-	✔	-	<1	-
Tachycardia	-	-	<1	-	<1	1
Central Nervous System						
Depression	-	-	-	-	1 to 4	-
Dizziness	-	-	1 to 3	-	<1	-
Fatigue	-	≥2	-	-	-	-
Headache	6.6	-	5 to 9	4	6	-
Insomnia	-	<1	<1	-	4	-
Nervousness	-	-	<1	-	-	-
Paresthesia	-	-	-	-	1 to 3	-
Tremor	-	-	<1	-	-	-
Dermatological						
Dry skin	-	-	-	-	<1	-
Rash	-	<1	<1	-	4	-
Pruritus	-	<1	<1	-	<1	-
Skin infection	-	-	-	-	<1	-
Skin ulcer	-	-	-	-	<1	-
Urticaria	-	-	<1	-	<1	-
Endocrine and Metabolic						
Diabetes	-	<1	-	-	-	-
Edema	-	-	-	-	3 to 5	-
Hypercholesterolemia	-	-	-	-	1 to 3	-
Hyperglycemia	-	-	-	-	1 to 3	-
Gastrointestinal						
Abdominal pain	-	≥2	-	-	5	1
Bitter taste	-	-	<1	-	-	-
Constipation	-	-	<1	-	1 to 5	-
Diarrhea	2.7	≥2	<1	-	-	-
Dyspepsia	-	-	1 to 5	-	1 to 6	-
Dysphagia	-	-	-	-	<1	-
Gastroenteritis	-	<1	-	-	-	-
Gastrointestinal pain	-	-	-	-	3 to 6	-
Gastrointestinal reflux	-	-	-	-	1 to 3	-
Gingivitis	-	-	-	-	<1	-
Intestinal obstruction	-	-	-	-	<1	-
Nausea	-	≥2	1 to 4	-	-	-
Stomatitis	-	-	-	-	1 to 3	-
Throat irritation	-	-	-	-	<1	-
Vomiting	1.1	<1	-	-	1 to 4	-
Xerostomia	-	-	2 to 4	-	5 to 16	-
Genitourinary						
Urinary retention	-	-	<1	✔	<1	-
Urinary tract infection	-	-	2 to 10	-	4 to 7	-
Musculoskeletal						
Arthralgia	-	≥2	-	-	4	2
Arthritis	-	-	<1	-	≥3	-
Back pain	-	≥2	2 to 7	2	-	-
Joint swelling	-	-	-	-	<1	-
Leg cramps	-	-	-	-	1 to 3	-
Myalgia	-	-	-	-	3 to 4	1
Skeletal pain	-	-	-	-	1 to 3	-
Respiratory						
Bronchitis	-	≥2	10 to 23	-	-	-
Bronchospasm	-	<1	2	✔	✔	-

Adverse Events	Aclidinium	Glycopyrrolate	Ipratropium	Revefenacin	Tiotropium	Umeclidinium
COPD exacerbation	-	-	8 to 23	-	-	-
Cough	3	<1	3 to 6	4	3	3
Dyspnea	-	≥2	7 to 10	-	-	-
Epistaxis	-	-	-	-	1 to 4	-
Laryngitis	-	-	-	-	1 to 3	-
Laryngospasm	-	-	<1	-	-	-
Nasopharyngitis	5.5	≥2	-	4	-	8
Oropharyngeal pain	-	2	-	-	-	-
Pharyngitis	-	-	4	-	7 to 13	1
Pneumonia	-	≥2	-	-	-	-
Rhinitis	1.6	≥2	2 to 6	-	3 to 6	-
Sinusitis	1.7	1	1 to 11	-	3 to 11	-
Sputum increased	-	-	1	-	-	-
Upper respiratory tract infection	-	2 to 3	9 to 34	3	41 to 43	1 to 5
Wheezing	-	≥2	-	-	-	-
Ocular						
Blurred vision	-	-	-	-	<1	-
Cataract	-	-	-	-	1 to 3	-
Eye pain	-	-	<1	-	-	-
Glaucoma	-	-	<1	-	<1	-
Intraocular pressure increased	-	-	-	-	<1	-
Mydriasis	-	-	<1	-	-	-
Narrow-angle glaucoma, worsening	-	-	-	✔	✔	-
Pupil dilation	-	-	-	-	<1	-
Other						
Accidents	-	-	-	-	5 to 13	-
Allergic skin reactions	-	-	✔	-	2 to 4	-
Anaphylactic reactions	-	-	<1	-	-	-
Angioedema	-	<1	<1	-	<1	-
Candidiasis	-	-	-	-	<1	-
Dehydration	-	-	-	-	<1	-
Dysphonia	-	-	-	-	1 to 3	-
Fall	1.1	-	-	-	-	-
Herpes zoster	-	-	-	-	1 to 3	-
Hypersensitivity reaction	-	<1	<1	✔	1 to 3	-
Infection	-	-	-	-	1 to 4	-
Influenza-like symptoms	-	-	2 to 8	-	3	-
Moniliasis	-	-	-	-	3 to 4	-
Toothache	1.1	-	-	-	-	1

✔ Percent not specified.
- Event not reported.
COPD=chronic obstructive pulmonary disease.

VII. Dosing and Administration

The usual dosing regimens for the inhaled antimuscarinics are listed in Table 7.

Table 7. Usual Dosing Regimens for the Inhaled Antimuscarinics[1-10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aclidinium	COPD: Dry powder inhaler: 1 inhalation twice daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 400 µg
Glycopyrrolate	COPD: Inhalation solution: 1 inhalation of contents of one vial twice daily	Safety and efficacy in children have not been established.	Inhalation solution: 25 µg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ipratropium	COPD: Aerosol inhaler: initial, 2 inhalations four times daily; maintenance, additional inhalations may be required; maximum, 12 inhalations in 24 hours Inhalation solution: 500 µg (1 unit dose vial) administered three to four times daily by oral nebulization, with doses 6 to 8 hours apart	Safety and efficacy in children have not been established.	Aerosol inhaler: 17 µg Inhalation solution: 0.2 mg/mL
Revefenacin	COPD: Inhalation solution: 175 µg (1 unit dose vial) administered once daily by oral nebulization	Safety and efficacy in children have not been established.	Inhalation solution: 175 µg/ 3 mL
Tiotropium	Asthma: Solution inhaler: 2 inhalations (1.25 µg each) once daily COPD: Dry powder inhaler: 2 inhalations of the powder contents of a single capsule once daily Solution inhaler: 2 inhalations (2.5 µg each) once daily	Asthma in patients ≥6 years: Solution inhaler: 2 inhalations (1.25 µg each) once daily	Dry powder inhaler: 18 µg Solution inhaler: 1.25 µg 2.5 µg
Umeclidinium	COPD: Dry powder inhaler: 1 inhalation once daily	Safety and efficacy in children have not been established.	Dry powder inhaler: 62.5 µg

COPD=chronic obstructive pulmonary disease.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the inhaled antimuscarinics are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Inhaled Antimuscarinics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Beeh et al.[19] (2014) Tiotropium Respimat 5 µg vs tiotropium Respimat 2.5 µg vs tiotropium Respimat 1.25 µg vs placebo	DB, PC, RCT, XO Patients 18 to 75 years of age with at least a 3-month history of asthma receiving medium-dose ICS (400 to 800 µg budesonide or equivalent dose) and a pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted	N=149 4 weeks	Primary: Peak FEV_1 response Secondary: Trough FEV_1, FEV_1 AUC(0-3h), FCV(0-3h), morning and evening PEF	Primary: The addition of tiotropium Respimat 5 µg, 2.5 µg or 1.25 µg to stable medium-dose ICS therapy was associated with improved lung function. At the end of the four-week treatment period, statistically significant differences from placebo in adjusted mean peak FEV_1(0-3h) responses were observed for all doses of tiotropium Respimat (P<0.0001 at all doses). The largest adjusted mean difference from placebo was observed with tiotropium Respimat 5 µg (188 mL; 95% CI, 140 to 236). Secondary: Trough FEV_1, FEV_1 AUC(0-3h), peak FVC(0-3h), trough FVC and FVC AUC(0-3h) responses with all doses of tiotropium Respimat were larger than the responses observed with placebo, and all were statistically significant except for trough FVC in the 1.25 µg group. Higher mean pre-dose PEF_{AM} responses were observed with all three tiotropium Respimat treatments compared with placebo (difference from placebo: 5 µg, 20.846 L/min; 2.5 µg, 17.895 L/min; 1.25 µg, 18.550 L/min; all P<0.0001). Higher mean pre-dose PEF_{PM} responses were also observed with all three tiotropium Respimat treatments compared with placebo (difference from placebo: 5 µg, 21.581 L/min; 2.5 µg, 14.577 L/min; 1.25 µg, 21.251 L/min; all P<0.0001). No significant differences in PEF_{AM} or PEF_{PM} responses were observed between the different tiotropium Respimat doses.
Paggiaro et al.[20] (2016) Tiotropium Respimat 5 µg or 2.5 µg	DB, PC, RCT Adults with symptomatic asthma receiving low- to medium-dose ICS (200 to 400 µg	N=464 12 weeks	Primary: Peak FEV_1 response Secondary: Adjusted mean trough FEV_1 and	Primary: After 12 weeks, both tiotropium Respimat doses were superior to placebo (adjusted mean difference from placebo: 5 µg, 128 mL; 2.5 µg, 159 mL; both P<0.001). Secondary: Both doses of tiotropium were also superior to placebo after 12 weeks

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	budesonide or equivalent dose) and a pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted		FEV_1 AUC(0-3h) responses, morning and evening PEF	with regard to the key secondary endpoint of adjusted mean trough FEV_1 response (adjusted mean difference from placebo: 5 µg, 122 mL, P=0.001; 2.5 µg, 110 mL, P=0.003). For other endpoints, both doses of tiotropium significantly improved FEV_1 AUC(0-3h), PEF_{AM}, and PEF_{PM} responses. The percentage of patients reporting adverse events was similar across the treatment groups.
Hamelmann et al.[21] (2016) Tiotropium Respimat 2.5 µg vs tiotropium Respimat 5 µg vs placebo	DB, PC, PG, RCT Patients 12 to 17 years of age with moderate symptomatic asthma who have been receiving maintenance therapy with ICSs with or without a LABA or an LTRA for four or more weeks before screening and have a pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted	N=398 48 weeks	Primary: Change in peak FEV_1 at week 24 Secondary: Trough FEV_1, FEV_1 AUC(0-3hr), FCV, time to first severe exacerbation, rescue medication use	Primary: A statistically significant greater improvement in peak FEV_1(0-3h) response was observed after 24 weeks with both doses of tiotropium versus placebo. The adjusted mean difference in response was greater with the 5 µg dose (174 mL; 95% CI, 76 to 272 mL) vs the 2.5 µg dose (134 mL; 95% CI, 34 to 234 mL). Secondary: Significant improvements in trough FEV_1 at week 24 were observed with the 5 µg dose only (P=0.03). Improvements in FEV_1 AUC(0-3h) for both the 5 and 2.5 µg doses compared with placebo were statistically significant, but the numerically higher values for peak FVC(0-3h), trough FVC, and FVC AUC(0-3h) with both tiotropium doses versus placebo did not reach statistical significance. Overall, 16 patients experienced at least one severe asthma exacerbation during the study: two (1.5%) in the 5 µg of tiotropium group, five (4.0%) in the 2.5 µg of tiotropium group, and nine (6.5%) in the placebo group. The weekly mean number of puffs of rescue medication used during the daytime, nighttime, and entire 24-hour period decreased over the 48-week treatment period but was statistically significant only with the 2.5 µg dose during the entire 24-hour period at week 48.
Vogelberg et al.[22] (2018) Tiotropium Respimat 2.5 µg vs tiotropium	DB, PG, MC, RCT Children 6 to 11 years of age with moderate symptomatic asthma who were treated with maintenance therapy of ICS at a	N=403 48 weeks	Primary: Change in peak FEV_1 at week 24 Secondary: Trough FEV_1 at week 24, peak FEV_1(0-3h) and trough FEV_1	Primary: Both doses of tiotropium provided improvements in peak FEV_1 response, measured as change from baseline, versus placebo at week 24, with an adjusted mean difference versus placebo for tiotropium 5 µg of 164 mL (95% CI, 103 to 225; P<0.001) and 170 mL for tiotropium 2.5 µg (95% CI, 108 to 231; P<0.001). Secondary: Statistically significant improvements were seen in trough FEV_1 at week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Respimat 5 µg vs placebo	stable medium dose (200 to 400 µg budesonide or equivalent) either alone or with a LTRA		responses at week 48, peak and trough FVC responses	24 for both doses: the adjusted mean difference from placebo was 118 mL for the 5 µg dose (95% CI, 48 to 188; P=0.001) and 116 mL for the 2.5 µg dose (95% CI, 46 to 186; P=0.001). Improvements in peak FEV_1(0-3h) and trough FEV_1 responses observed at week 24 were sustained to week 48, with P values <0.05 for each comparison.
Szefler et al.[23] (2017) Tiotropium Respimat 2.5 µg vs tiotropium Respimat 5 µg vs placebo	DB, MC, PG, RCT Children 6 to 11 years of age with severe symptomatic asthma who have been receiving maintenance therapy with ICSs either at a stable high dose in combination with ≥1 controller medications (e.g., LABA or LTRA) or at a stable medium dose in combination with ≥2 controller medications (e.g., LABA and/or LTRA and/or sustained-release theophylline) for four or more weeks before screening and have a pre-bronchodilator FEV_1 ≥60% and ≤90% of predicted	N=401 12 weeks	Primary: Change in peak FEV_1 at week 12 Secondary: Trough FEV_1, FEV_1 AUC(0-3hr), FCV; weekly mean asthma symptom-free days response; weekly mean rescue medication use response	Primary: Tiotropium provided a statistically significant improvement versus placebo in the primary end point, peak FEV_1(0-3h) response at week 12, with the 5 µg dose (adjusted mean difference, 139 mL; 95% CI, 75 to 203; P<0.001) but not with the 2.5 µg dose (adjusted mean difference, 35 mL; 95% CI, −28 to 99; P=0.27); all subsequent analyses were therefore considered descriptive. Secondary: Improvements in trough FEV_1 response versus placebo after 12 weeks of treatment were statistically significant with the 5 µg dose (adjusted mean difference, 87 mL; 95% CI, 19 to 154; P=0.01) but not with the 2.5 µg dose (adjusted mean difference, 18 mL; 95% CI, −48 to 85; P=0.59). No statistically significant differences compared with placebo were observed for adjusted mean peak FVC(0-3h) and trough FVC responses at week 12 following treatment with either dose of tiotropium. The adjusted mean number of asthma symptom-free days was increased by a similar degree in all treatment groups after 12 weeks, and there was a nonsignificant difference versus placebo in adjusted mean daytime rescue medication use with both tiotropium doses.
Wechsler et al.[24] (2015)	MC, OL, PG, RCT	N=1070	Primary: Time to first	Primary: There was no difference between LABA + ICS vs tiotropium + ICS in time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BELT LABA (salmeterol 50 µg or formoterol 9 µg, depending on the initial prescription by the treating physician) BID vs tiotropium 18 µg QD Each in addition to the patient's prior dose of ICS	Self-identified black patients 18 to 75 years of age with asthma who were receiving, or eligible for, step 3 or step 4 combination ICS and LABA therapy according to National Heart, Lung, and Blood Institute asthma guidelines	6 to 18 months (mean of 310 days)	exacerbation Secondary: Patient-reported outcomes, FEV_1, rescue medication use, adverse events	to first exacerbation (mean number of exacerbations/person-year, 0.42 vs 0.37 (rate ratio, 0.90; 95% CI, 0.73 to 1.11; log-rank P=0.31). Secondary: Patient-reported outcomes scores all improved within both groups (P<0.001), but there was no difference between groups. There was also no between-group difference in change in lung function as measured by FEV_1 over the course of the entire study, nor at the 12-month time point (0.003 L for LABA + ICS vs −0.018 L for tiotropium + ICS; P=0.33) or 18-month time point (−0.053 L for LABA + ICS vs −0.078 L for tiotropium + ICS; P=0.49). There was no difference in average rescue medication use, which decreased when compared with baseline rescue medication use in both groups. The percentage of patients experiencing non–asthma-related or asthma-related adverse events and serious adverse events did not differ between treatments (2% of LABA + ICS patients vs 3% of tiotropium + ICS patients; P=0.16).
Peters et al.[25] (2010) Tiotropium 18 µg QD and beclomethasone 80 µg BID vs beclomethasone 160 µg BID vs beclomethasone 80 µg and salmeterol 50 µg BID	DB, RCT, XO Patients ≥18 years of age with asthma, FEV_1 >40% predicted, and non-smoking status (<10 pack-years)	N=210 52 weeks	Primary: Morning PEF Secondary: FEV_1 before bronchodilation, number of asthma-control days, asthma symptoms, rescue-therapy use, asthma exacerbations, use of health services, biomarkers of airway inflammation, results of validated questionnaires	Primary: Patients receiving tiotropium had a morning PEF that was 25.8 L/min higher than that of patients receiving beclomethasone 160 µg twice daily (95% CI, 14.4 to 37.1; P=0.001). There were no significant differences between tiotropium treatment and salmeterol treatment with respect to the morning PEF, which was 6.4 L/min higher among patients receiving tiotropium (95% CI, -4.8 to 17.5; P=0.26). Secondary: Compared to the administration of beclomethasone 160 µg twice daily, the addition of tiotropium to beclomethasone improved most secondary outcomes, including evening PEF (P=0.001), proportion of asthma control days (P=0.01), FEV_1 before bronchodilation (P=0.004), and daily symptom scores (P=0.001). The addition of tiotropium to beclomethasone increased the pre bronchodilator FEV_1 more than the addition of salmeterol (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lazarus et al.[26] (2019) Mometasone twice-daily (at a dose of 220 µg with the Asmanex Twisthaler or 200 µg with the Asmanex HFA), vs tiotropium once-daily (at a dose of 5 µg with Spiriva Respimat vs placebo twice-daily	DB, MC, XO Patients ≥12 years of age who had mild, persistent asthma. Patients were categorized according to the sputum eosinophil level (<2% or ≥2%)	N=295 42 weeks	Primary: Response (determined according to a hierarchical composite outcome that incorporated treatment failure, asthma control days, and the FEV_1) among patients with a low sputum eosinophil level who had a prespecified differential response to one of the trial agents; a two-sided P-value <0.025 denoted statistical significance Secondary: A comparison of results in patients with a high sputum eosinophil level and those with a low level	Primary: A total of 73% of the patients had a low eosinophil level; of these patients, 59% had a differential response to a trial agent. However, there was no significant difference in the response to mometasone or tiotropium, as compared with placebo. Among the patients with a low eosinophil level who had a differential treatment response, 57% (95% CI, 48 to 66) had a better response to mometasone, and 43% (95% CI, 34 to 52) had a better response to placebo (P=0.14). In contrast 60% (95% CI, 51 to 68) had a better response to tiotropium, whereas 40% (95% CI, 32 to 49) had a better response to placebo (P=0.029). Secondary: Among patients with a high eosinophil level, the response to mometasone was greater than the response to placebo (74% vs 26%) but the response to tiotropium was not (57% vs 43%).
COPD				
Jones et al.[27] (2012) ATTAIN Aclidinium 200 µg	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD	N=828 24 weeks	Primary: Change from baseline in trough FEV_1 at 24 weeks	Primary: After 24 weeks of treatment, the mean trough FEV_1 was significantly higher in patients treated with aclidinium 200 µg (99±22 mL; P<0.0001) or 400 µg (128±22 mL; P<0.0001) when compared to patients treated with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs aclidinium 400 µg BID vs placebo	and an FEV_1/FVC <70% and FEV_1 <80% who were current or former smokers with a ≥10 pack-years history		Secondary: Change from baseline in peak FEV_1 at 24 weeks, proportion of patients experiencing clinically significant improvements in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) scores at 24 weeks	Secondary: At 24 weeks, the mean change from baseline in peak FEV_1 was significantly higher in patients treated with aclidinium 200 µg (185±23 mL) or 400 µg (209±24 mL) compared to patients receiving placebo (P<0.0001 for both). A significantly higher proportion of patients treated with aclidinium 200 or 400 µg experienced a clinically significant improvement in SGRQ score when compared to patients treated with placebo at 24 weeks (56.0 and 57.3 vs 41.0%; P<0.001 for both). A significantly greater proportion of patients treated with aclidinium 200 or 400 µg achieved a clinical improvement in TDI score when compared to patients treated with placebo at 24 weeks (53.3 and 56.9 vs 45.5%; P≤0.05 for both). After 24 weeks, the mean total daily use of relief medication was significantly lower with aclidinium 200 (0.61 inhalations/day; P=0.0002) or 400 µg (0.95 inhalations/day; P<0.0001) compared to placebo; however, this was not a pre-specified endpoint. The rates of COPD exacerbations of any severity were decreased with both aclidinium 200 and 400 µg compared to placebo; however, this was not statistically significant and was not a pre-specified endpoint.
Kerwin et al.[28] (2012) ACCORD COPD I Aclidinium 200 µg BID vs aclidinium 400 µg BID	DB, PC, PG, RCT Patients ≥40 years of age diagnosed with moderate to severe stable COPD and a post-bronchodilator FVC <70% and FEV_1 ≥30% and <80% predicted and who were current or	N=561 12 Weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Change from baseline in peak FEV_1 at week 12, FEV_1 on day one, trough and peak FEV_1 at weeks	Primary: Treatment with aclidinium 200 or 400 µg significantly increased trough FEV_1 from baseline compared to patients receiving placebo (86 and 124 mL, respectively; P<0.0001 for both). Secondary: Treatment with aclidinium 200 or 400 µg significantly increased the peak FEV_1 from baseline compared to patients receiving placebo (146 and 192 mL, respectively; P<0.0001 for both). There was a statistically significant improvement from baseline in peak FEV_1 at week 12 for patients receiving aclidinium 200 or 400 µg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	former smokers with a ≥10 pack-years history		one, four and eight, $AUC_{0\text{-}3/3h}$ FEV_1, trough, peak and $AUC_{0\text{-}3/3h}$ FVC and trough IC at 12 weeks, changes in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) at weeks four, eight and 12, nighttime symptoms, COPD exacerbations and safety	compared to patients receiving placebo (P<0.0001 for both). The changes from baseline in trough and peak FEV_1 were significantly higher in all aclidinium treatment groups at all-time points evaluated compared to the placebo group (P<0.0001 for all). Patients randomized to receive aclidinium 200 or 400 µg experienced statistically significant increases in $AUC_{0\text{-}3/3h}$ FEV_1 compared to the placebo group (144 and 192 mL, respectively; P<0.0001 for both). At 12 weeks, a statistically significant improvement in peak FVC within three hours after dosing occurred for the aclidinium 200 (312 mL; P<0.0001) and 400 µg (359 mL; P<0.0001) groups compared to those randomized to placebo. Compared to the placebo group, there was a significant improvement from baseline in trough IC in both the aclidinium 200 (48 mL; P<0.001) and 400 µg (67 mL; P<0.0001) groups. At week four, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ score compared to treatment with placebo (-3.2 and -3.6, respectively; P<0.001 for both). At study end, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ scores compared to treatment with placebo (- 2.7 and -2.5, respectively; P=0.013 and P=0.019, respectively). At 12 weeks, a higher proportion of patients receiving aclidinium 200 µg experienced a decrease ≥4 units in SGRQ compared to patients receiving placebo (P<0.05); however, there was no difference in responder rates between patients receiving aclidinium 400 µg or placebo. At 12 weeks, a higher proportion of patients receiving aclidinium 200 or 400 µg achieved a clinically meaningful improvement (≥1 unit) in TDI scores compared to the placebo group (P<0.05 for both). Compared to placebo, patients receiving either dose of aclidinium experienced significantly improved nighttime COPD symptoms (P<0.05 for both). At week 12, there was a statistically significant decrease in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				number of nighttime awakenings in the aclidinium 400 µg group compared to the placebo group (P<0.05). A reduction in the rate of moderate to severe COPD exacerbations per-patient per-year was observed with aclidinium 200 and 400 µg compared to placebo (33 and 34%, respectively; P>0.05 for both); however, these results were not statistically significant. The incidence of adverse events was similar between the aclidinium and placebo groups. Treatment-emergent adverse events occurred in 44.7% of patients receiving aclidinium 400 µg, 50.5% of those receiving aclidinium 200 µg and 52.2% of the placebo group. A COPD exacerbation was the only adverse effect that was reported in >5% of patients in all groups, with a lower incidence in the aclidinium 400 µg group compared to the aclidinium 200 µg and placebo groups.
Rennard et al.[29] (2013) ACCORD COPD II Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, PG, RCT Patients ≥40 years of age, current or former smokers (i.e., smoking history ≥10 pack-years), and diagnosed with stable moderate-to-severe COPD	N=542 12 weeks	Primary: Change from baseline to week 12 in morning pre-dose (trough) FEV_1 Secondary: Change from baseline to week 12 in peak FEV_1	Primary: Changes from baseline in trough FEV_1 at week 12 were significantly greater for aclidinium 200 and 400 µg versus placebo, with LSM treatment differences (95% CI) over placebo of 51 (8 to 94) mL and 72 (29 to 115) mL, respectively (both P<0.05). Secondary: Aclidinium-treated patients showed greater improvements over placebo in peak FEV_1 change from baseline at week 12 (both P<0.0001). Aclidinium 400 µg consistently provided greater improvements in all lung function outcomes versus aclidinium 200 µg throughout the study. Improvements from baseline were observed with aclidinium in SGRQ total score (200 µg, -6.0; 400 µg, -5.4) and Transition Dyspnea Index (TDI) focal score (200 µg, 1.0; 400 µg, 1.3). Clinically important improvements in SGRQ total and TDI focal scores were achieved by 45 and 51% of patients, respectively, who received aclidinium 400 µg, with a significant difference vs placebo for TDI (P<0.05). Anticholinergic-related adverse events (e.g., dry mouth) were infrequent, occurring <2% for any event in any treatment group. Both aclidinium doses were well tolerated.
Wise et al.[30] (2019)	DB, MC, RCT	N=3,589	Primary: Time to first	Primary: The number of patients who experienced an adjudicated composite MACE

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ASCENT-COPD Aclidinium 400 µg BID vs placebo	Patients ≥40 years of age with COPD (FEV_1/FVC ratio <0.70 and FEV_1 <70% predicted), smoking history of ≥10 pack-years, and a history of cardiovascular disease or cardiac risk factors	Up to 3 years	adjudicated MACE (i.e., irrespective of treatment exposure; with MACE defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), annual rate of moderate to severe COPD exacerbations during the first year of the study Secondary: Exacerbations that required hospitalization	was 69 (3.9%) in the aclidinium group vs 76 (4.2%) in the placebo group. The Cox regression HR was 0.89 (1-sided 97.5% CI, 0 to 1.23), which did not cross the prespecified noninferiority margin of 1.8. The annual rate of moderate to severe exacerbations during the first year of treatment was lower in patients treated with aclidinium vs placebo by on-treatment analysis (aclidinium, 0.44; placebo, 0.57; rate ratio, 0.78; 2-sided 95% CI, 0.68 to 0.89; P<0.001). Secondary: The rate of COPD exacerbations requiring hospitalization was reduced with aclidinium vs placebo in the on-treatment analysis (0.07 vs 0.10, respectively; rate ratio, 0.65; 2-sided 95% CI, 0.48 to 0.89; P=0.006).
Gelb et al.[31] (2013) Aclidinium 200 µg BID vs aclidinium 400 µg BID	DB, PG, RCT Patients ≥40 years of age, current or former smokers (i.e., smoking history ≥10 pack-years), and diagnosed with stable moderate-to-severe COPD	N=602 52 weeks	Primary: Safety (adverse events, laboratory tests, vital signs, and 12-lead electrocardiograms Secondary: Efficacy (spirometry, SGRQ, rescue medication use)	Primary: The percentage of patients reporting adverse events was similar for 200 µg (62.4%) and 400 µg (66.0%) groups, with most being mild to moderate in severity. Commonly reported adverse events (≥3% in total patient population) included nasopharyngitis, cough, sinusitis, headache, nausea, and upper respiratory infection. Secondary: Mean improvements from baseline in trough FEV_1 were observed during the first assessed time point at Week One (200 µg, 64 mL; 400 µg, 91 mL), with maximum improvements of 64 mL (Week One) and 101 mL (Week 24) for the 200 µg and 400 µg doses, respectively. Clinically important improvements in SGRQ total scores (≥4-point improvement from baseline) were observed at all study visits throughout the 52-week treatment period with aclidinium 200 µg and 400 µg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Singh et al.[32] (2012) Aclidinium 100 µg BID vs aclidinium 200 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID vs placebo	AC, DB, DD, MC, PC, XO Patients ≥40 years of age with a diagnosis of stable moderate to severe COPD and a FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history	N=79 7 days (each treatment arm had a 5 to 9 day washout period)	Primary: Mean change from baseline in FEV_1 $AUC_{0–12}$ on day seven Secondary: Change from baseline in FEV_1 $AUC_{12–24}$, FEV_1 $AUC_{0–24}$, trough FEV_1 on day seven, FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at day seven, morning peak FEV_1 on day one and seven, morning trough FVC on day seven, use of relief medication after seven days and safety	Primary: The change from baseline in FEV_1 $AUC_{0–12}$ on day seven compared to placebo was 154 mL for the aclidinium 100 µg group, 176 mL for the aclidinium 200 µg group, 208 mL for the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group (P<0.0001 for all compared to placebo). Aclidinium 400 µg was associated with statistically significant improvements in FEV_1 $AUC_{0–12}$ compared to the 100 µg dose (P<0.01) while the difference between patients receiving aclidinium 400 µg or formoterol 12 µg was not significantly different. Secondary: Improvements in FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–24}$ at day seven were significantly greater for all doses of aclidinium and formoterol compared to the placebo group (P<0.0001 for all). There was no difference between treatment with aclidinium 400 µg and formoterol with regard to changes in FEV_1 $AUC_{0–24}$. Patients treated with aclidinium 400 µg experienced a statistically significant improvement in FEV_1 $AUC_{12–24}$ compared to treatment with formoterol (56 mL; P<0.01). Compared to placebo the mean change from baseline in trough FEV_1 was 106, 114 and 154 and 148 mL with aclidinium 100, 200 and 400 µg, and formoterol, respectively (P<0.0001 for all compared to placebo). Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{0-12} compared to patients treated with placebo (243, 254, 274, and 301 mL, respectively; P<0.001 for all) on day seven. Following seven days of treatment, patients receiving aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{12–24}$ compared to patients receiving placebo (260, 255, 302, and 383 mL, respectively; P<0.001 for all). Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{0–24}$ compared to patients treated with placebo (251, 255, 283, and 338 mL, respectively; P<0.001 for all) on day seven.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				After seven days of treatment, patients receiving aclidinium 100 µg, 200 µg, and 400 µg or formoterol demonstrated a statistically significant increase in morning peak FEV_1 on day one (140, 176, 223, and 221 mL, respectively; P<0.0001 for all) and day seven (189, 201, 242, and 246 mL, respectively; P<0.0001 for all) compared to placebo. Patients treated with aclidinium 100, 200, and 400 µg or formoterol demonstrated a statistically significant increase in morning trough FVC (147, 191, 218, and 213 mL, respectively; P<0.001 for all) on day seven compared to patients treated with placebo. Patients treated with aclidinium 100, 200, and 400 µg or formoterol required significantly fewer daily inhalations of rescue medication compared to patients treated with placebo (-0.27, -0.39, -0.48, and -0.67, respectively; P<0.05 for all). The majority of adverse events were mild or moderate in severity and more prevalent in the placebo group (P value not reported). Four serious adverse events were reported, but none was treatment-related. There were no clinically relevant changes in laboratory parameters, and the incidence of ECG abnormalities was similar between placebo and active treatments.
Beier et al.[33] (2013) Aclidinium 400 µg BID vs tiotropium 18 µg QD vs placebo	DB, DD, RCT Patients ≥40 years of age with a diagnosis of stable moderate to severe COPD and a FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history	N=414 6 weeks	Primary: Change from baseline in normalized FEV_1 AUC over the 24-hour period post-morning dose ($AUC_{0–24}$) Secondary: Change from baseline in normalized FEV_1 AUC over the nighttime period	Primary: In the primary endpoint analysis, FEV_1 $AUC_{0–24}$ was significantly improved with aclidinium compared with placebo at week 6 (P<0.0001). Compared with placebo, tiotropium also significantly increased FEV_1 $AUC_{0–24}$ from baseline to week 6 (P<0.0001); the effects of aclidinium and tiotropium over six weeks were similar. Secondary: FEV_1 $AUC_{12–24}$ and FEV1 $AUC_{0–12}$ were also significantly increased from baseline with both aclidinium and tiotropium vs placebo (P<0.0001). There were no differences between active treatment groups. When asked ‘which device do you prefer?’ at week six, significantly more patients overall preferred Genuair to HandiHaler (80.1 vs 10.7%; P<0.0001). Inhaler preference appeared to be independent of whether

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			($AUC_{12–24}$), additional changes in FEV_1 and FVC, inhaler preference, safety	active medication or placebo was administered via the inhalers. Adverse event incidence was similar in the placebo (25.9%), aclidinium (27.5%), and tiotropium (29.7%) groups.
LaForce et al.[34] (2016) GEM1 Glycopyrrolate 15.6 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable but symptomatic moderate to severe COPD according to the 2011 GOLD Guidelines, with airflow limitation of ≥30% and <80% of the predicted normal (FEV_1), post-bronchodilator FEV_1/FVC <0.70, current or ex-smokers who had a smoking history of ≥10 pack years and an mMRC grade ≥2	N=441 12 weeks	Primary: Change from baseline in FEV_1 $AUC_{0 \text{ to } 12h}$ at week 12 Secondary: Change in trough FEV_1, change from baseline in the health status assessed by SGRQ, change from baseline in the percentage of days without rescue medication use	Primary: The glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo. The change from baseline LS mean was 0.125 L in the glycopyrrolate group compared to -0.014 L in the placebo group (treatment difference LS Mean, 0.139 L; 95% CI, 0.095 to 0.184; P<0.001). Secondary: Greater improvement in trough FEV_1 occurred in the glycopyrrolate group vs the placebo group at all assessed time points from day two (LSM treatment difference, 0.115 L; P<0.001) until week 12 (LSM treatment difference, 0.115 L; P<0.001). The improvement in SGRQ total score from baseline at week 12 with glycopyrrolate was greater than placebo (LSM treatment difference −2.8 units; 95% CI, −5.0 to −0.5; P=0.016). The SGRQ responder rate (defined as an improvement in score of ≥4) was 49% for the glycopyrrolate group compared to 41% for the placebo group (OR, 1.43; 95% CI, 0.95 to 2.15, P=0.083). Patients treated with glycopyrrolate received less daily rescue albuterol during the trial compared to patients treated with placebo. The percentage of days without rescue medication use was LS Mean 16.6 for the glycopyrrolate group versus 10.5 for placebo (P<0.027). Adverse events were comparable for the glycopyrrolate and placebo groups.
Kerwin et al.[35] (2016) GEM2 Glycopyrrolate	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable	N=432 12 weeks	Primary: Change from baseline in FEV_1 $AUC_{0 \text{ to } 12h}$ at week 12	Primary: The glycopyrrolate group demonstrated a larger increase in mean change from baseline in FEV_1 $AUC_{0 \text{ to } 12 \text{ h}}$ compared to placebo. The change from baseline LS mean was 0.115 L in the glycopyrrolate group compared to -0.008 L in the placebo group (treatment difference LS Mean, 0.123 L;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15.6 µg BID vs placebo	but symptomatic moderate to severe COPD according to the 2011 GOLD Guidelines, with airflow limitation of ≥30% and <80% of the predicted normal (FEV_1), post-bronchodilator FEV_1/FVC <0.70, current or ex-smokers who had a smoking history of ≥10 pack years and an mMRC grade ≥2		Secondary: Change in trough FEV_1, change from baseline in the health status assessed by SGRQ, change from baseline in the percentage of days without rescue medication use	95% CI, 0.081 to 0.165; P<0.001). Secondary: Differenced in trough FEV_1 between the glycopyrrolate group and the placebo group were significant (P<0.001) at each visit during the treatment period. The SGRQ responder rate (defined as an improvement in score of ≥4) was 55% for the glycopyrrolate group compared to 42% for the placebo group (OR, 1.78; 95% CI, 1.17 to 2.71; P<0.01). Patients treated with glycopyrrolate received less daily rescue albuterol during the trial compared to patients treated with placebo. The change from baseline in the use of rescue medication was significantly lower in daily (treatment difference -0.53 puffs/day; P<0.05), daytime (treatment difference -0.30 puffs/day; P<0.05), and nighttime (treatment difference -0.25 puffs/night; P<0.05) number of puffs in patients treated with glycopyrrolate compared with placebo over the 12-week treatment period. Adverse events were reported for 111 (51.4%) patients in the glycopyrrolate group versus 91 (42.5%) patients in the placebo group.
Mahler et al.[36] (2016) GEM3 Glycopyrrolate 15.6 µg BID vs indacaterol 75 µg QD	DB, MC, PG, RCT Patients ≥40 years of age with stable but symptomatic moderate to severe COPD according to the 2011 GOLD Guidelines, with airflow limitation of ≥30% and <80% of the predicted normal (FEV_1), post-bronchodilator FEV_1/FVC <0.70, current or ex-	N=511 52 weeks	Primary: Adverse events Secondary: Time to first moderate or severe COPD exacerbations, measurement of vital signs, ECG, laboratory evaluations	Primary: Overall, the incidence of adverse events was comparable between the glycopyrrolate (77.3%) and indacaterol (77.0%) groups. A majority of adverse events reported in both the treatment groups were mild (20.3%) or moderate (43.4%) in severity and occurred at comparable rates. The incidence of suspected drug-related adverse events was low and comparable between both the groups (glycopyrrolate, 12.4%; indacaterol, 9.0%). Secondary: Over 52 weeks of treatment, no significant differences were found between the treatment groups for the incidence of moderate or severe COPD exacerbations (incidence rate ratio, 0.92; 95% CI, 0.65 to 1.29; P=0.625). Moreover, the time to first moderate or severe COPD exacerbation was also comparable across both the treatment groups (hazard ratio, 0.92; 95% CI, 0.64 to 1.31; P=0.636).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	smokers who had a smoking history of ≥10 pack years and an mMRC grade ≥2			The change from baseline in the pre-dose trough FEV_1 (an average of the two FEV_1 measurements 45 and 15 min pre-dose) was analyzed at all post-baseline visits; no statistically significant differences were observed between the two treatments at any visit. At the end of the treatment period, the change from baseline in the pre-dose FEV_1 was also comparable between the groups (glycopyrrolate, 0.056 L; indacaterol, 0.060 L; treatment difference, −0.004 L, P=0.902). There were no clinically meaningful differences between the two treatment groups for any of the vital signs (pulse rate and, systolic and diastolic blood pressure), and hematology, biochemistry, or urinalysis parameters.
Martinez et al.[37] (2017) PINNACLE-1 and PINNACLE-2 Glycopyrrolate-formoterol 18-9.6 µg BID vs glycopyrrolate 18 µg BID vs formoterol 9.6 µg BID vs placebo BID or tiotropium 18 µg QD (OL	DB, MC, PC, RCT Patients 40 to 80 years of age with moderate-to-very severe COPD, a smoking history of at least 10 pack-years, and a postbronchodilator FEV_1/FVC ratio <0.70 and FEV_1 <80% predicted	N=2,103 (PINNACLE-1) N=3,125 (PINNACLE-2) 24 weeks	Primary: Change from baseline in morning predose trough FEV_1 at week 24 Secondary: Change from baseline in morning predose trough FEV_1 over 24 weeks, peak change from baseline in FEV_1 within two hours postdose at week 24, time to onset of action on day one, change from baseline in SGRQ total score, and change from baseline in average	Primary: At week 24, differences in change from baseline in the morning predose trough FEV_1 for glycopyrrolate-formoterol vs placebo, glycopyrrolate, and formoterol were 150 mL, 59 mL, and 64 mL in PINNACLE-1 (all P<0.0001) and 103 mL, 54 mL, and 56 mL in PINNACLE-2 (all P<0.001), respectively. Secondary: The change from baseline in morning predose trough FEV_1 over 24 weeks was similar but with slightly larger estimated differences vs placebo. For peak change from baseline in FEV_1 within two hours postdose at week 24, glycopyrrolate-formoterol showed significant differences vs placebo and monocomponents in both PINNACLE-1 and PINNACLE-2 (all P<0.0001). The change from baseline in peak FEV_1 within two hours postdose over 24 weeks was similar. For onset of action on day one, glycopyrrolate-formoterol showed a significant difference from placebo at five minutes, which was the first time point assessed in both studies, with respective differences of 187 mL and 186 mL (all P<0.0001). In PINNACLE-1 only, glycopyrrolate-formoterol showed significant differences in SGRQ total score at week 24 vs placebo (–2.52) and glycopyrrolate MDIs (–2.33). Glycopyrrolate-formoterol-treated patients were more likely to achieve the minimum clinically important difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
comparator in PINNACLE-1 only)			daily rescue albuterol use	of 4 units in SGRQ total score vs glycopyrrolate and placebo in PINNACLE-1 (all P<0.05). In PINNACLE-1 and PINNACLE-2, glycopyrrolate-formoterol showed a significant reduction in rescue albuterol use over 24 weeks vs placebo (–1.08 and –1.04 puffs/day, respectively). In PINNACLE-2, a significant reduction vs glycopyrrolate (–0.57) was seen, with nominal significance vs formoterol (–0.29).
Mahler et al.[38] (2015) FLIGHT1 and FLIGHT2 Indacaterol-glycopyrrolate (27.5-15.6 µg BID) vs indacaterol (27.5 µg BID) vs glycopyrrolate (15.6 µg BID) vs placebo	DB, MC, RCT (pooled analysis of 2 identical trials) Patients ≥40 years of age with stable but symptomatic moderate-to-severe COPD	N=2,038 12 weeks	Primary: FEV_1 $AUC_{0\text{-}12\ hrs}$ Secondary: Change in SGRQ total score from baseline, transition dyspnea index total score, rescue medication use	Primary: At Week 12, treatment with indacaterol-glycopyrrolate demonstrated greater improvement in FEV_1 $AUC_{0–12h}$ when compared with its respective monocomponents in the pooled analysis (treatment difference, 103 mL and 88 mL vs indacaterol and glycopyrrolate, respectively; P<0.001) and in the individual studies. In addition, indacaterol-glycopyrrolate, indacaterol, and glycopyrrolate all demonstrated a greater improvement in FEV_1 $AUC_{0–12h}$ when compared with placebo (P<0.001). Secondary: Statistically and clinically meaningful improvements in SGRQ total score, transition dyspnea index total score, and reduction in rescue medication use were observed with indacaterol-glycopyrrolate compared with placebo (P<0.001). The safety profile was comparable across the treatment groups.
Ikeda et al.[39] (1995) Ipratropium 40 µg via MDI vs ipratropium 80 µg	DB, PC, RCT, XO Adult male patients with stable COPD with a history of >20 pack-years of cigarette smoking, and FEV_1 <60% and a FEV_1/FVC <70%,	N=26 5 separate visits over a period of 1 month	Primary: Change from baseline in FEV_1, FVC and the difference in adverse reactions reported Secondary:	Primary: All treatment groups showed a significant improvement in FEV_1 and FVC when compared to the placebo group at all-time points evaluated (P<0.01). Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV_1 (P<0.05 and P<0.01). The lower dose combination was significantly different in FVC response

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
via MDI vs ipratropium 40 µg via MDI and albuterol 200 µg via MDI vs ipratropium 80 µg via MDI and albuterol 400 µg via MDI vs placebo	and chest radiographic findings compatible with pulmonary emphysema		Not reported	from the low-dose monotherapy (P<0.01), but not high-dose monotherapy. No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects (no P value reported). Secondary: Not reported
Matera et al.[40] (1996) Ipratropium 40 µg QID and salmeterol 50 µg BID vs ipratropium 40 µg QID vs salmeterol 50 µg BID	RCT, SB, XO Male patients ≥40 years of age with COPD and an FEV_1 between 16 and 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in FEV_1 AUC	Primary: The peak response (28.8±5.0%) for salmeterol was greater than that for ipratropium (26.0±9.1%), but equivalent peak bronchodilation occurred with salmeterol and ipratropium plus salmeterol (28.0±4.2). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared to placebo (P<0.05), but only salmeterol and ipratropium plus salmeterol induced a significant (P<0.05) spirometric increase over the 12 hour monitoring period. Secondary: The AUC for active treatments were significantly increased compared to placebo (P<0.05), and salmeterol and ipratropium plus salmeterol significantly increased FEV_1 compared to ipratropium alone (P<0.05). There was no significant difference (P>0.05) between the salmeterol and ipratropium plus salmeterol AUC.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Van Noord et al.[41] (2000) Ipratropium 40 µg QID and salmeterol 50 µg BID vs salmeterol 50 µg BID vs placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with COPD, a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication use, PEF, clinic lung function, adverse events and exacerbations	Primary: After inhalation of salmeterol, there was a mean±SEM peak increase in FEV_1 7.0±0.7% predicted after two hours. After 12 hours, the improvement was 2.0±1.0% of predicted value. Ipratropium plus salmeterol produced a peak increase in FEV_1 11.0±0.8% of predicted after two hours. After 12 hours, the improvement was 3.0±0.8% of predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary: Throughout the treatment period there was a mean±SEM decrease in the daytime symptom score from 1.9±0.1 to 1.7±0.1 in the placebo group (P value not significant), from 2.0±0.1 to 1.4±0.1 (P<0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (P<0.001) in the ipratropium plus salmeterol group. Compared to placebo, salmeterol and ipratropium plus salmeterol was associated with a higher percentage of days and nights without the use of additional albuterol (P<0.01). No difference was observed between the two active treatment groups (P=0.35). Improvements in morning PEF were significantly greater in both active treatment groups compared to the placebo group (P<0.001), while there was no difference between the salmeterol and the ipratropium plus salmeterol treatment groups with regard to morning PEF. The improvements in evening PEF were greater in both active treatment arms compared to the placebo arm (P<0.001), whereas the improvement was better in the ipratropium plus salmeterol group compared to the salmeterol group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				During the 12-week treatment period, the mean±SEM increase in FEV_1 was 1.0±0.9% of predicted for placebo, 5.0±0.9% of predicted for salmeterol, and 8.0±0.8% for ipratropium plus salmeterol. All differences were statistically significant (P<0.01). The change in FVC was 4.0±1.2% of predicted with placebo, 7.0±1.2% of predicted with salmeterol and 12.0±1.2% with ipratropium plus salmeterol. The differences between ipratropium plus salmeterol and salmeterol alone and between ipratropium plus salmeterol and placebo were both significant (P<0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (P=0.055). The reported incidence and nature of possible and probably drug-related adverse events were similar among the three groups. During the 12-week treatment period, 35 patients experienced a COPD exacerbation, 18 (36%) patients in the placebo group, 11 (23%) patients in the salmeterol group, and six (13%) patients in the ipratropium plus salmeterol group. The only significant difference was between the ipratropium plus salmeterol group and the placebo group (P<0.01).
Bone et al.[42] (1994) Ipratropium 21 µg QID via MDI vs albuterol 100 µg QID via MDI vs ipratropium and albuterol 21-100 µg QID via MDI (fixed-dose combination	DB, MC, PG, PRO, RCT Patients ≥40 years of age diagnosed with COPD with stable disease, relative stable, moderately severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio ≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score and safety Secondary: Not reported	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (P<0.001 to P=0.015). There was no difference in symptom score between the groups (P value not reported). Compared to either agent alone, the overall FVC response was significantly greater in the combination group (P<0.01 to P=0.04). There were no significant differences between any of the treatment groups in terms of adverse effects or safety (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
product)	for COPD control			
Dorinsky et al.[43] (1999) Ipratropium 36 µg QID via MDI vs albuterol 180 µg QID via MDI vs equivalent dose of ipratropium and albuterol via MDI (fixed-dose combination product)	DB, MC, PG, RETRO, RCT Patients ≥40 years of age with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤70%	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as an increase in FEV_1 of 12 and 15% from baseline) Secondary: Not reported	Primary: The percentage of patients demonstrating a 15% increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the ipratropium and albuterol group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day one and two ($P<0.05$). The overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from two to eight percent (P value not reported). A significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in the ipratropium and albuterol group compared to the individual treatment groups ($P<0.05$). Secondary: Not reported
Friedman et al.[44] (1999) Ipratropium 36 µg QID via MDI vs albuterol 180 µg QID via MDI vs equivalent dose of ipratropium and albuterol via MDI (fixed-dose	DB, MC, PG, RETRO, RCT Patients ≥40 years of age diagnosed with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during three months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤70%	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC_{0-4h} Secondary: Not reported	Primary: A statistically significant improvement in FEV_1 in the ipratropium and albuterol group was observed compared to other treatment groups on all test days ($P<0.01$). A significantly higher FEV_1 AUC_{0-4} in the ipratropium and albuterol group compared to the other treatment groups was observed on all test days ($P\leq0.008$). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination product)				
Zuwallack et al.[45] (2010) Ipratropium and albuterol 20-100 µg QID, administered via Respimat® inhaler (fixed-dose combination product) vs ipratropium and albuterol 36-206 µg QID, administered via aerosol MDI (Combivent®) (fixed-dose combination product) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a 2 week run-in phase with ipratropium	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack- years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium and albuterol via Respimat® inhaler vs aerosol MDI and ipratropium and albuterol via Respimat® inhaler vs ipratropium via Respimat® inhaler Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC AUC_{0-6}, $_{0-4}$ and $_{4-6}$; peak FVC response on day one, 29, 57 and 85 and safety	Primary: On day 85, ipratropium and albuterol Respimat® inhaler was NI to ipratropium and albuterol aerosol MDI at zero to six hours, and was significantly more effective to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium and albuterol Respimat® inhaler was non inferior to ipratropium Respimat® inhaler. Ipratropium and albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all test days. Secondary: Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium and albuterol Respimat® inhaler and ipratropium and albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium and albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium and albuterol aerosol MDI (172 to 219 minutes) overall. Median duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (N=358), 74 (N=357) and 63% (N=295) of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.				ipratropium and albuterol Respimat® inhaler, ipratropium and albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event was lower with ipratropium/albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium/albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium/albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
McCrory et al.[46] (2002) Ipratropium vs β-agonists, combination of β-agonists and ipratropium, or placebo	MA (9 RCTs) Adult patients with a diagnosis of COPD, symptoms consistent with an acute exacerbation	N=525 Duration ranged from 1 hour to 14 days	Primary: Short-term changes in FEV_1, WMD of long-term effects on FEV_1 Secondary: Not reported	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported). The change in FEV_1 was not significant when ipratropium was added to a β_2-adrenergic agonist (WMD, 0.02 L; 95% CI, -0.08 to 0.12). These results were similar 24 hours post-dose (long-term) between the ipratropium and β_2-adrenergic agonist groups (WMD, 0.05 L; 95% CI, -0.14 to 0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Ferguson et al.[47] (2019) Revefenacin 88 µg once daily in the morning via nebulizer vs revefenacin 175 µg once daily in the morning via nebulizer vs placebo	2 identical DB, RCTs Patients ≥40 years of age with moderate to very severe COPD, a smoking history of ≥10 pack years, a post-ipratropium FEV_1/FVC ratio of <0.7 and a post-ipratropium FEV_1 of <80% of predicted	N=619 (Study 0216) N=611 (Study 0217) 12 weeks	Primary: Change from baseline in trough FEV_1 at day 85 Secondary: Overall treatment effect on trough and peak FEV_1 on day 1, adverse events	Primary: Revefenacin (88 µg and 175 µg) improved day 85 baseline-adjusted mean trough FEV_1 compared with placebo in both Study 0126 and Study 0127. In Study 0126, the placebo-adjusted least squares (LS) mean increase in trough FEV_1 was 79.2 mL for revefenacin 88 µg (P=0.0003) and 146.3 mL for revefenacin 175 µg (P<0.0001). In Study 0127, the LS mean increase in trough FEV_1 with revefenacin was 160.5 mL (88 µg) and 147.0 mL (175 µg) (both P<0.0001). Analysis of pooled Study 0126 and Study 0127 results revealed placebo-adjusted increases in trough FEV_1 of 119.8 mL (88 µg) and 148.1 mL (175 µg), respectively; the 28.3 mL difference in trough FEV_1 between the revefenacin 88 µg and 175 µg doses was not statistically significant (P=0.088). Secondary: Revefenacin increased overall treatment effect trough FEV_1 by ≥ 100 mL compared with placebo in both studies. Analysis of pooled study results revealed placebo-adjusted increases in overall treatment effect FEV_1 of 115.3 mL (88 µg) and 142.3 mL (175 µg). In addition, revefenacin increased trough FEV_1 by ≥100 mL on days 15, 29, 57, 84 and 85 versus placebo at both the 88 µg and 175 µg dose. A significant increase in FEV_1 occurred within two hours of the first treatment with revefenacin in both studies. Analysis of pooled study results revealed placebo-adjusted LS mean increases in peak FEV_1 (0 to 2 hours after first dose) of 127.3 mL (88 µg) and 129.5 mL (175 µg) (both P<0.0001). The overall incidence of treatment-emergent adverse events was similar in the revefenacin (88 µg and 175 µg) and placebo treatment groups for both studies. Approximately 47% to 57% of patients by treatment group reported at least one adverse event. COPD (worsening/exacerbation) was the highest-incidence adverse event (≤12.2%). Headache (≤6.8%), respiratory infection (≤6.6%), dyspnea (≤5.7%) and cough (≤5.1%) were the next most common adverse events, with similar frequencies between treatment groups.
Donohue et al.[48] (2019)	Partially DB, PG, RCT	N=1,055 52 weeks	Primary: Safety and tolerability	Primary: Any treatment-emergent adverse event occurred in 74.7% of the revefenacin 88 µg group, 72.2% of the revefenacin 175 µg group, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Revefenacin 88 µg once daily in the morning via nebulizer vs revefenacin 175 µg once daily in the morning via nebulizer vs OL active control tiotropium 18 µg via HandiHaler	Patients ≥40 years of age with moderate to very severe COPD, a smoking history of ≥10 pack years, a post-ipratropium FEV_1/FVC ratio of <0.7 and a post-ipratropium FEV_1 of <80% of predicted		Secondary: Not reported	77.2% of the tiotropium group. Adverse events were considered related to study drug for 53 (14.6%) patients who received revefenacin 88 µg, 45 (13.4%) who received revefenacin 175 µg, and 42 (11.8%) who received tiotropium. Of the adverse events considered related to study drug, severity was rated as moderate or severe for 36 (9.9%), 28 (8.4%), and 24 (6.7%) patients, in the revefenacin 88 µg, 175 µg, and tiotropium groups, respectively. COPD exacerbation or worsening was the most frequent adverse events in all groups (26.5%), and occurred at a lower proportion in the revefenacin 175 µg group (21.8%) than in the other two treatment groups (revefenacin 88 µg, 29.4%; tiotropium, 28.1%). The estimated yearly rate of any exacerbation (mild, moderate, or severe) was 0.38 events/year for revefenacin 175 µg, compared with higher rates of 0.57 events/year for revefenacin 88 µg and 0.46 events/year for TIO (P=NS). Secondary: Not reported
Donohue et al.[49] (2019) Revefenacin 88 µg once daily in the morning via nebulizer vs revefenacin 175 µg once daily in the morning via nebulizer vs OL active control tiotropium 18 µg	Partially DB, PG, RCT Patients ≥40 years of age with moderate to very severe COPD, a smoking history of ≥10 pack years, a post-ipratropium FEV_1/FVC ratio of <0.7 and a post-ipratropium FEV_1 of <80% of predicted	N=1,055 52 weeks	Primary: Change in trough FEV_1, changes in health outcomes using general and COPD-specific respiratory symptom rating instruments, concomitant use of rescue medications Secondary: Not reported	Primary: Both doses of revefenacin, as well as tiotropium, elicited statistically significant (all P<0.0003) improvements from baseline in trough FEV_1. The trough FEV_1 profile for revefenacin 175 µg (range, 52.3 to 124.3 mL) was similar to that of tiotropium (range, 79.7 to 112.8 mL) up to Month nine, but diverged after that, in part due to differences in subject discontinuation in the final three months of the trial. There was a statistically significant (P<0.05) improvement in SGRQ, COPD Assessment Test, and Clinical COPD Questionnaire at all time points assessed from three months for all three treatment arms. Evaluation of rescue albuterol use showed an average of least squares mean (standard error) values of 1.6 (0.23), 1.9 (0.2) and 1.3 (0.21) puffs per day over the 12-month treatment period in the revefenacin 175 µg, revefenacin 88 µg, and tiotropium groups, respectively. However, there was a consistent trend toward a decrease in puffs per day in all treatment groups throughout the study. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
via HandiHaler				Not reported
Casaburi et al.[50] (2005) Tiotropium 18 µg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD and a FEV_1 ≤60% of predicted normal and a FEV_1/FVC ≤70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ and rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time compared to patients receiving placebo. The difference between the treatments was 1.65 minutes (P=0.183). Patients receiving tiotropium experienced significantly longer exercise endurance times compared to patients receiving placebo after 13 weeks of treatment (including eight weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 (P=0.025) and 6.60 minutes (P=0.018), respectively. The mean increase in endurance time from day 29 before PR to day 92 after PR was 80% in the tiotropium group and 57% in the placebo group (P value not reported). Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for placebo. On day 176, the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatment groups was 1.67 units (P=0.03; differences exceeding one unit were considered clinically meaningful). The SGRQ total score in the tiotropium group was lower (i.e., improved) on each test day compared to the placebo group. After PR, the SGRQ scores improved by 7.27 units in the tiotropium group compared to 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (P value not reported). On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication/day when compared to patients receiving placebo over 25 weeks of treatment (P<0.05).
Tashkin et al.[51] (2008) UPLIFT Tiotropium 18 µg	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-	N=5,993 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and	Primary: The rate of decline in the mean post bronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug as compared to those who completed the study period. There were no significant differences between the tiotropium group and the placebo group in the rate of decline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo	severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less		post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	in the mean value for FEV_1 either pre bronchodilator (P=0.95) or post bronchodilator (P=0.21) from day 30 to the end of study-drug treatment. Secondary: There were no significant differences between the treatment groups in the rate of decline in the mean value for FVC either pre bronchodilator (P=0.30) or post bronchodilator (P=0.84). The rate of decline in the mean value for SVC was not reported. Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (P<0.0001), although these differences on average were below what is considered to have clinical significance. The overall mean between-group difference in SGRQ total score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium (P<0.001). Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (P value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (P value not reported). During the four year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the four year study period plus 30 days included in the intent-to-treat analysis, 941 patients died; 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02).
Decramer et al.[52] (2009) UPLIFT Tiotropium 18 µg QD	Subgroup analysis of UPLIFT Patients ≥40 years of age with moderate-to-very-	N=2,739 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-	Primary: Rate of decline of mean post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group (P=0.024). Rate of decline of mean pre-bronchodilator FEV_1 did not differ between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.	severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less		bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Secondary: Mean values for pre- and post-bronchodilator FEV_1 were higher in the tiotropium group at all time points (P<0.0001). Mean pre-bronchodilator FVC and SVC were higher in the tiotropium group at all time points (P<0.001). Mean post-bronchodilator FVC was significantly higher in the tiotropium group at all time points (P<0.01). No significant difference in mean post-bronchodilator SVC was observed between groups. Health status was better in the tiotropium group compared to the placebo group for all time points (P≤0.006). Time to first exacerbation and time to exacerbation resulting in hospital admission were longer in the tiotropium group (HR, 0.82; 95% CI, 0.75 to 0.90 and 0.74; 95% CI, 0.62 to 0.88 respectively). Risk of mortality from lower respiratory tract conditions and from all causes were lower for the tiotropium group though differences between groups were not significant.
Troosters et al.[53] (2010) UPLIFT Tiotropium 18 µg QD vs placebo Subgroup analysis of patients in the	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and	Primary: After 30 days of treatment, pre-bronchodilator FEV_1 was significantly larger in the tiotropium group compared to the placebo group (P<0.0001). Trough FEV_1 remained significantly larger in the tiotropium group compared to the placebo group at all time points throughout the trial (P<0.05). Secondary: No significant differences between groups were observed in pre- or post-FVC (P≥0.81). Pre- and post-SVC was significantly higher in the tiotropium group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
UPLIFT trial who were not on other maintenance treatment at randomization.			SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	(P≤0.046). The improvement in the SGRQ scores was significantly higher in the tiotropium group compared to the placebo group in the first six months of treatment (P=0.0065). SGRQ total score declined more slowly in the tiotropium group compared to the placebo group (P=0.002). No statistically significant difference in exacerbation rate was observed between groups (P=0.08). No statistically significant difference in time to first exacerbation was observed between groups (P=0.24). No statistically significant difference in exacerbations leading to hospitalizations was observed between groups.
Burgel et al.[54] (2014) UPLIFT Tiotropium 18 µg QD vs placebo Cluster analysis of patients in the UPLIFT trial based on age, BMI, FEV_1, smoking, and SGRQ score.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after broncho-dilation and a FEV_1/FVC 70% or less	N=5706 4 years	Primary: Exacerbations, hospitalizations, mortality Secondary: Not reported	Cluster 1 (low-risk) (N=820) contained GOLD Stage 2 or 3 patients, who were heavy smokers and had relatively preserved HRQoL, but high rates of comorbidities. Cluster 2 (N=2339) contained mostly GOLD Stage 2 patients with moderate HRQoL impairment and very low rates of comorbidities. Cluster 3 (high-risk) (N=1022) contained 81% of GOLD Stage 3 and 4 patients, with severe HRQoL impairment, high pack-years, and high rates of comorbidities. Compared with cluster 3, cluster 4 (N=1525) contained patients with less severe airflow limitation, slightly less severe HRQoL impairment, and fewer pack-years and comorbidities. Primary: Tiotropium significantly reduced exacerbations rates and also increased time to first exacerbation in each cluster. Rates of severe exacerbations (leading to hospitalization) were significantly reduced in cluster 3 (P<0.05), which had the highest rate of exacerbations leading to hospitalization, but not in other clusters. The beneficial effect of tiotropium on all-cause mortality in the overall

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				population (HR, 0.87; 95% CI, 0.75 to 1.00; P=0.054) was explained by a 21% reduction in cluster 3 (P=0.07), with no effect in other clusters. Secondary: Not reported
Halpin et al.[55] (2009) Tiotropium 18 µg QD vs placebo	Pooled analysis of 9 RCTs Patients ≥40 years of age with stable COPD, FEV_1 ≤65% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=6,171 ≥24 weeks	Primary: Proportion of patients with COPD exacerbation, proportion of patients with hospitalization due to COPD exacerbation, time to first COPD exacerbation, time to first hospitalization for exacerbation Secondary: Not reported	Primary: Tiotropium reduced the risk of COPD exacerbation by 21% compared to placebo (95% CI, 0.729 to 0.862; P<0.0001). Tiotropium reduced the risk of hospitalization associated with COPD exacerbation by 21% compared to placebo (95% CI, 0.65 to 0.96; P=0.015). The cumulative incidence rate of COPD exacerbation at 46 weeks was 42.1% for tiotropium compared with 50.8% for placebo (P<0.001). The cumulative incidence rate of hospitalizations associated with COPD exacerbation at 46 weeks was 8.5% for tiotropium compared with 10.8% for placebo (P=0.015). The protective effect of tiotropium was consistent regardless of age, gender, ICS use, and disease severity. Secondary: Not reported
Wise et al.[56] (2013) TIOSPIR Tiotropium handihaler 18 µg QD vs tiotropium respimat 2.5 µg	DB, PG, RCT Patients ≥40 years of age with COPD, FEV_1 ≤70% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=17,183 Mean follow-up of 2.3 years	Primary: Time to death from any cause, risk of first COPD exacerbation Secondary: Number of COPD exacerbations, time to first moderate or severe exacerbation, time	Primary: For the risk of death from any cause, the HR for Respimat 5 µg vs HandiHaler was 0.96 (95% CI, 0.84 to 1.09); for Respimat 2.5 µg vs HandiHaler, the HR was 1.00 (95% CI, 0.87 to 1.14). For the risk of the first exacerbation, the HR for Respimat 5 µg vs HandiHaler was 0.98 (95% CI, 0.93 to 1.03; P=0.42). Secondary: Rates of exacerbations, moderate or severe exacerbations, and severe exacerbations were similar in the three study groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs tiotropium respimat 5 µg QD			to and number of severe exacerbations, time to first major cardiovascular event	The overall incidence of major adverse cardiovascular events was 3.9, 3.9, and 3.6% in the Respimat 2.5-µg, Respimat 5-µg, and HandiHaler groups, respectively.
Troosters et al.[57] (2014) Tiotropium 18 µg QD vs placebo All patients received p.r.n. albuterol	DB, MC, PC, PG, RCT Patients with moderate (GOLD stage II) COPD previously naive to maintenance therapy	N=457 24 weeks	Primary: FEV_1 AUC from 0 to 3 hours (AUC_{0-3h}) post-dose response at week 24 Secondary: FEV_1 and FVC parameters, physical activity, patient and physician assessments	Primary: For the primary endpoint at week 24, tiotropium was superior to placebo (0.19±0.27 vs −0.03±0.22 l; least-squares (LS) mean difference 0.23 l; 95% CI, 0.18 to 0.27; P<0.001). Secondary: The corresponding mean change from baseline to week 24 values for FVC AUC_{0-3h} were 0.23±0.47 l for tiotropium and −0.06±0.37 l for placebo (LS mean difference tiotropium vs placebo 0.31 l; 95% CI, 0.24 to 0.38; P<0.001). At week 24 the mean increase from baseline in peak FEV_1 and FVC were significantly higher with tiotropium than with placebo (P<0.001). While physical activity levels were higher numerically in the tiotropium group than in the placebo group, they were not statistically significantly different. At week 24, patients treated with tiotropium were more frequently classified by their physician as 'excellent' than those in the placebo group (18.1 vs 10.9%) and were less frequently classified as 'poor/fair' compared with the placebo group (19.0 vs 25.4%), signifying improved health status with tiotropium vs placebo (P=0.045 at week 24).
Kerstjens et al.[58] (2012) Tiotropium 2.5 µg 2 inhalations QD via Respimat® inhaler vs	DB, PC, PG, RCT Patients 18 and 75 years of age and at least a 5 year history of asthma that was diagnosed before the age of 40 years, with a score	N-912 48 weeks	Primary: Peak and trough FEV_1 at 24 weeks, time to first severe asthma exacerbation Secondary: Peak and trough	Primary: At 24 weeks, the mean±SE change in peak FEV_1 was significantly greater in the tiotropium group compared to placebo in each trial with a difference of 86±34 mL in trial 1 (P=0.01) and 154±32 mL in trial 2 (P<0.001). The predose trough FEV_1 also significantly improved in each trial in the tiotropium group compared to placebo with a difference of 88±31 mL in trial 1 (P=0.01) and 111±30 mL in trial 2 (P<0.001), respectively. The average time to first severe asthma exacerbation was increased by 56 days with tiotropium relative to placebo, corresponding to an overall risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Individual pretrial maintenance therapy consisting of high dose glucocorticoids and LABAs was maintained throughout the study. Trial looked at two separate replicate trials (trial 1 and trial 2).	of 1.5 on Asthma Control Questionnaire 7, FEV_1 ≤80% than predicted value and FVC ≤70% 30 minutes after inhalation of a short acting beta agonist, despite daily therapy with inhaled glucocorticoids and LABAs		FEV_1 at each treatment visit, AUC (for three hours after administration of study drug), time to first worsening of asthma, Asthma Control Questionnaire 7	reduction of 21% (HR, 0.79; P=0.03). Secondary: Improvements in peak FEV_1 were maintained over 48 weeks (P≤0.05 and P≤0.001 in trials 1 and 2, respectively). The mean difference in trough FEV_1 change from 24 to 48 weeks between tiotropium and placebo was 42 (95% CI, -21 to 104) and 92 (95% CI, 32 to 151) in trials 1 and 2, respectively. The median time to first worsening of asthma was increased by 134 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 31% (HR, 0.69; P<0.001). A minimally important difference for the Asthma Control Questionnaire 7 was not achieved in either trial.
Canto et al.[59] (2012) Tiotropium 18 µg QD via Handihaler® vs placebo All patients were receiving formoterol 12 µg BID.	DB, PC, PRO, RCT, XO Patients with stable COPD (defined by GOLD) with a long history of smoking (>20 pack-years); patients were randomized to each treatment group for a 2 week treatment period, followed by a 7 day washout period and then patients XO for a second 2 week period of the alternative regimen	N=38 5 weeks	Primary: Pulmonary function tests (FEV_1, FVC, IC, EELV), inspiratory muscle strength, constant work exercise test Secondary: Not reported	Primary: Treatment with formoterol and tiotropium resulted in a greater numeric improvement in FEV_1 (1.07±0.25 to 1.25±0.32) compared to treatment with formoterol and placebo (1.09±0.21 to 1.21±0.29), although both groups achieved a statistically significant improvement (P<0.05). Similarly, patients treated with formoterol and tiotropium achieved a numerically greater increase in FVC (2.51±0.57 to 2.75±0.91) compared to patients treated with formoterol and placebo (2.55±0.66 to 2.66±0.98), although a statistically significant improvement was observed in both groups (P<0.05). The increase in IC was greater in the formoterol and tiotropium group (1.68±0.41 to 2.16±0.77) compared to the formoterol and placebo group (1.66±0.45 to 2.02±0.49), although both groups achieved a statistically significant improvement (P<0.05). Patients treated with formoterol and tiotropium achieved a greater numeric improvement in EELV (4.35±0.77 to 3.98±0.67) compared to patients treated with formoterol and placebo (4.34±0.59 to 3.85±0.77), although

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				both groups achieved a statistically significant improvement (P<0.05). Treatment with formoterol and tiotropium resulted in a statistically significant improvement in the maximal inspiratory pressure at rest, immediately after exercise and during recovery, while formoterol and placebo improved the maximal inspiratory pressure only at the 10 minute time point during recovery. Treatment with formoterol and tiotropium resulted in significantly larger increments in the maximal inspiratory pressure at all points of comparison. The time to the limit of tolerance was improved following two weeks of intervention in both groups, however, treatment with formoterol and tiotropium resulted in a greater increase compared to treatment with formoterol and placebo (40.7±7.6% vs 84.5±8.2%; P<0.05). Secondary: Not reported
Van Noord et al.[60] (2000) Tiotropium 18 µg QD vs ipratropium 40 µg QID	DB, DD, MC, PG Patients with stable COPD with mean age of 65 years and average FEV_1 41% of predicted values	N=288 15 weeks	Primary: Changes in FEV_1 and FVC Secondary: Daily records of PEF, use of albuterol	Primary: The FEV_1 response, at all time points on days eight, 50 and 92, was significantly greater following tiotropium compared to ipratropium (differences of 0.09, 0.11, and 0.08 L; P<0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than ipratropium. The differences in trough FEV_1 values were most pronounced (P<0.001), whereas differences in peak FEV_1 increase did not reach statistical significance (P>0.05). Secondary: The improvement in both morning and evening PEF was greater in the tiotropium group than in the ipratropium group. The difference in morning PEF between the groups was statistically significant up through week 10 (P<0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (P<0.05). In both groups, there was a drop in the use of rescue albuterol, the reduction being greater in the tiotropium group than in the ipratropium group (P<0.05).
Vincken et al.[61]	DB, DD, MC, PG,	N=535	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Tiotropium 18 µg QD vs ipratropium 40 µg QID	RCT Patients with COPD ≥40 years of age with an FEV_1 ≤65% of predicted normal value and ≤70% of FVC	12 months	Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared to 20 mL for the ipratropium group. Tiotropium was more effective compared to ipratropium at all time points on all test days except for the first two hours following the first dose and up to one hour after the dose, one week later (P<0.05). At the end of one year, trough FEV_1 was 120 mL above the day one baseline for patients receiving tiotropium, and had declined by 30 mL for those receiving ipratropium (difference of 150 mL between groups; P<0.001 at all time points). The FVC results paralleled the FEV_1 results. At the end of one year, the trough FVC was 320 mL above the day one baseline for patients receiving tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups). Secondary: Throughout the one-year treatment period, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group (P<0.01 at all weekly intervals). On average, patients receiving tiotropium self-administered approximately four fewer inhalations of albuterol/week compared to patients receiving ipratropium (P<0.05 for 40 of the 52 weeks). The BDI focal scores for the two groups were comparable. Tiotropium significantly improved all components of the TDI on all test days compared to ipratropium (P<0.05). The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement ≥1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; P=0.004). During the one-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30±1.13 on day 364; P<0.05). Quality of life, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last two test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.
Kawasumi et al.[62] (2013) Tiotropium vs ipratropium	Cohort New patients with COPD (≥45 years of age) with a first hospital admission for COPD	N=3,723 Up to 6 months	Primary: Hospital readmission for COPD Secondary: Not reported	Primary: Among the subset of 1,500 matched patients, 215 (14.3%) were readmitted to hospital within six months. There was no statistically significant group difference in hospital readmissions using both Pearson and Spearman correlation coefficients (HR, 0.98; 95% CI, 0.72 to 1.34; OR, 0.97; 95% CI, 0.70 to 1.36). Secondary: Not reported
Yohannes et al.[63] (2011) Tiotropium vs ipratropium vs LABA (salmeterol or formoterol)	MA (16 RCTs) Trials lasting ≥12 weeks that compared tiotropium to placebo, ipratropium, or LABAs in patients ≥40 years of age with a diagnosis of COPD	N=16,301 Up to 52 months	Primary: SGRQ and TDI scores, exacerbations, exacerbation-related hospitalizations and adverse events Secondary: Not reported	Primary: The proportion of patients achieving a clinically important improvement in SGRQ scores was greater with tiotropium compared to placebo (OR, 1.61; 95% CI, 1.38 to 1.88; P<0.001). Patients receiving tiotropium were also more likely to experience improvements in SGRQ scores compared to patients receiving ipratropium (OR, 2.03; 95% CI, 1.34 to 3.07; P<0.001). There was no significant difference when tiotropium was compared to salmeterol (OR, 1.26; 95% CI, 0.93 to 1.69; P=0.13). There were statistically greater odds of achieving a clinically significant change in TDI score with tiotropium compared to placebo (OR, 1.96; 95% CI, 1.58 to 2.44; P<0.001). In addition, there were significantly greater odds of improving TDI scores associated with tiotropium compared to ipratropium (OR, 2.10; 95% CI, 1.28 to 3.44; P=0.003); however, there was no significant difference when tiotropium was compared to salmeterol (OR, 1.08; 95% CI, 0.80 to 1.45; P=0.61). Tiotropium significantly reduced the risk of exacerbations compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (OR, 0.83; 95% CI, 0.72 to 0.94; P=0.004) and ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92; P=0.02). A reduction in exacerbations was observed in the two studies that compared tiotropium to salmeterol; however, the difference was not statistically significant (OR, 0.86; 95% CI, 0.67 to 1.11; P=0.25). Patients receiving tiotropium were less likely to have an exacerbation-related hospitalization compared to patients receiving placebo (OR, 0.89; 95% CI, 0.80 to 0.98; P=0.02). There was a nonsignificant reduction in the odds of an exacerbation-related hospitalization with tiotropium compared to ipratropium (OR, 0.59; 95% CI, 0.32 to 1.09; P=0.09), salmeterol (OR, 0.54; 95% CI, 0.29 to 1.00; P=0.051) and formoterol (OR, 4.98; 95% CI, 0.58 to 42.96; P=0.15). The number of patients who experienced a serious adverse event was not statistically significant when tiotropium was compared to placebo (OR, 1.06; 95% CI, 0.97 to 1.17; P=0.19) Only one study compared tiotropium to salmeterol, reporting a significantly lower risk of a serious adverse event with tiotropium (OR, 0.39; 95% CI, 0.16 to 0.95; P=0.04). Secondary: Not reported
Donohue et al.[64] INHANCE (2010) Tiotropium 18 µg QD vs indacaterol 150 µg QD vs indacaterol 300 µg	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history of ≥20 pack-years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Trough FEV_1 at 12 weeks, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and safety	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified minimum clinically important difference of 120 mL (P value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority (P≤0.01) and non-inferior (P<0.001). FEV_1 at five minutes post dose on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium (P<0.001 for all vs placebo and for indacaterol vs tiotropium).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs placebo Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.				TDI total scores significantly increased relative to placebo (P<0.001 for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks (P<0.05 for all). Over 26 weeks, the change from baseline in mean daily number of inhalations of as-needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (P<0.001 for both). Significantly fewer inhalations of as-needed albuterol were required with either indacaterol dose compared to tiotropium (P≤0.001 for both). The proportion of days with no use of as-needed albuterol was significantly lower with both doses of indacaterol compared to placebo (P<0.001 for both) and tiotropium (P≤0.001). The change from baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (P<0.001 for all) and tiotropium (morning; P≤0.001 for both, evening; P<0.05 and P<0.01). The proportion of nights with no awakenings (P<0.01 for both), days with no daytime symptoms (P<0.05 for both) and days able to perform usual activities (P<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved with both doses of indacaterol at all assessments compared to the placebo treatment group (P<0.01 for all) but not compared to tiotropium (P value not reported). Analysis of time to first COPD exacerbation showed a reduced risk with indacaterol 150 µg compared to placebo (HR, 0.69; 95% CI, 0.51 to 0.94; P=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; P=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; P=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments.
Decramer et al.[65] (2013) INVIGORATE	MC, PG, RCT Patients aged ≥40 years with severe	N=3444 52 weeks	Primary: To investigate whether indacaterol was	Primary: The estimated least squares mean trough FEV_1 difference between the groups was −0.011 L (least squares mean with indacaterol 1.134 L [SE 0.008] vs tiotropium 1.145 L [0.008]; one-sided 97.5% CI lower limit

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tiotropium 18 µg QD vs indacaterol 150 µg QD	COPD and a history of at least one moderate to severe exacerbation in the previous 12 months		non-inferior to tiotropium for trough FEV_1 at week 12 Secondary: Rate of exacerbations at week 52	−0.026 L; P<0.0001). The lower limit of the 97.5% CI was above the prespecified non-inferiority margin of −0.055 L, suggesting that indacaterol was non-inferior to tiotropium. Secondary: Indacaterol did not show non-inferiority in terms of exacerbation rates: 0.79 (indacaterol) versus 0.61 (tiotropium); ratio 1.29 (one-sided 97.5% CI upper limit 1.44). In the safety set, we recorded no between-group difference in the number of patients who had adverse events.
Mahler et al.[66] (2015) Tiotropium 18 µg vs indacaterol 150 µg	Pooled analysis of 2 RCTs Patients ≥40 years of age with GOLD groups A (fewer symptoms) or B (more symptoms) COPD: mild or moderate airflow limitation (FEV_1 ≥50% predicted), with fewer than two exacerbations in the past year (not requiring hospitalization)	N=1422 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Transition Dyspnea Index (TDI), SGRQ, use of rescue mediation	Primary: After 12 weeks, the difference in trough FEV_1 between indacaterol and tiotropium was 0.03 L (95% CI, 0.01 to 0.05; P=0.002). Secondary: Greater improvements occurred in the indacaterol group than the tiotropium group across all outcomes. In 'GOLD A' patients not receiving ICS, differences favored indacaterol vs tiotropium (trough FEV_1 0.05 L; rescue medication use −0.41 puffs/day; TDI total score 0.94 points; SGRQ total score −3.13 units, all P<0.01). In 'GOLD B, no ICS' patients, compared with tiotropium, indacaterol treatment increased trough FEV_1 (0.055 L, P<0.05) and permitted a larger reduction in rescue medication use (−0.81 puffs/day, P=0.004).
Niewoehner et al.[67] (2009) Tiotropium 18 µg QD vs ipratropium and albuterol MDI QID (fixed-dose	Pooled analysis of 2 RCTs Patients ≥40 years of age with COPD, current or former cigarette smoker with lifetime consumption of ≥10 pack-years, postbronchodilator	N=676 12 weeks	Primary: Trough FEV_1, FEV_1 $AUC_{0–6}$, and FVC Secondary: PEF, albuterol rescue therapy, total albuterol use, and patient global evaluations	Primary: Mean change in trough FEV_1 was significantly larger in the tiotropium group compared to the ipratropium and albuterol group (difference, 86 mL; 95% CI, 49 to 133 mL; P<0.0001). Mean FEV_1 $AUC_{0–6}$ in the tiotropium arm was statistically non-inferior to the ipratropium and albuterol arm (difference, 17 mL; 95% CI, -21 to 56 mL; P=0.0003), but not statistically superior (P=0.37). Mean peak FEV_1 responses were larger in the ipratropium/albuterol arm compared with the tiotropium arm, with differences ranging from 120 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination product) Concomitant medications allowed throughout the trial included ICSs, theophylline, and stable doses of prednisone (not to exceed 10 mg daily or its equivalent)	FEV_1 ≤70% of predicted, pre bronchodilator FEV_1 ≤65% of predicted, and FEV1/FVC ≤70% who were receiving ipratropium and albuterol (18-103 µg) MDI for ≥1 month			134 mL (P<0.001). Differences in FVC responses were similar to those observed with the FEV_1. Mean FVC trough for the tiotropium group was significantly larger on study days 42 and 84 (P<0.01) compared with the ipratropium and albuterol group, but the AUC_{0-6} was not (P>0.5). Secondary: Weekly mean morning PEF and FEV_1 were both significantly larger in the tiotropium arm compared with the ipratropium and albuterol arm for morning measurements (P<0.05), but not for evening measurements. No significant treatment-related differences were detected in albuterol rescue therapy, physician global evaluations, or patient reported shortness of breath. Total albuterol use was significantly lower in the tiotropium group compared to the ipratropium/albuterol group (5.3 vs 6.8 puffs per day based on weekly means; P<0.001). Mean patient global evaluations were statistically significantly better (P<0.05) for the tiotropium group on study day 42, but not on study day 84.
Tashkin et al.[68] (2009) Tiotropium 18 µg QD vs arformoterol 15 µg BID vs arformoterol 15 µg	MC, PG, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity ≥2 on Medical Council Dyspnea Score, pre bronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65%	N=234 2 weeks	Primary: Difference in mean FEV_1 AUC_{0-24} Secondary: Differences in rescue therapy use and occurrence of adverse events	Primary: Mean FEV_1 AUC_{0-24} improved to a similar degree with arformoterol (0.10 L) and tiotropium (0.08 L), and was greater with combination therapy (0.22 L; all P<0.005). Peak FEV_1, peak FVC, 24-hour trough FEV_1, and IC also improved to a similar degree with arformoterol and tiotropium, and were greatest with combination therapy. Dyspnea (mean transition dyspnea index) improved to a similar degree with arformoterol (2.3) and tiotropium (1.8), and was greatest with combination therapy (3.1; all P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID and tiotropium 18 µg QD	predicted			Levalbuterol use decreased for all treatment groups (range -1.8 to -2.5 actuations per day). All treatments had similar overall frequencies of adverse events: arformoterol (25.0%), tiotropium (27.5%) and combination (30.8%).
Van Noord et al.[69] (2005) Tiotropium 18 µg QD for 6 weeks vs formoterol 12 µg BID for 6 weeks vs tiotropium 18 µg QD and formoterol 12 µg BID for 6 weeks	DB, RCT, XO Patients with COPD	N=71 18 weeks	Primary: FEV_1, FVC, rescue medication use Secondary: Not reported	Primary: Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0-12 h) than formoterol (127 vs 86 mL). The average nighttime FEV_1 (12-24 h) was not different among the treatment groups (tiotropium 43 mL and formoterol 38 mL). Combination therapy had significantly greater improvements in both endpoints compared to monotherapy (daytime 234 mL and nighttime 86 mL). Changes in FVC were similar to the changes in FEV_1 results. Daytime salbutamol use was significantly lower with combination therapy compared to monotherapy (tiotropium plus formoterol 1.81 puffs/day, tiotropium 2.41 puffs/day, formoterol 2.37 puffs/day). Secondary: Not reported
Covelli et al.[70] (2015) Tiotropium bromide 18 µg inhaled QD via DPI vs fluticasone furoate and vilanterol 100/25 µg inhaled QD via DPI	AC, DB, DD, PG, RCT Patients ≥ 40 years of age with a diagnosis of COPD, ≥ 10 pack-year smoking history, FEV_1 30% to 70% of predicted, FEV_1 to FVC ratio ≤ 70%, and either CVD or a CVD risk factor other than smoking.	N= 623 12 weeks	Primary: Change from baseline in 24-hour weighted mean FEV_1 on day 84 Secondary: Time to onset of bronchodilation, trough FEV_1, rescue medication use, SGRQ-C scores, CAT measures, CVD related	Primary: Both fluticasone furoate/vilanterol and tiotropium improved the 24-hour weighted mean FEV_1 from baseline after 12 weeks (LS mean change 117 mL and 95 mL respectively) with no significant difference between treatment groups (difference of 0.022 L; 95% CI, -0.012 to 0.055; P=0.201). Secondary: The median time to onset of bronchodilation was 17.0 minutes with fluticasone furoate/vilanterol compared to 20.5 minutes with tiotropium. The change from baseline in FEV_1 trough level did not differ significantly between treatment groups (difference of 0.005L; 95% CI, -0.029 to 0.039). More subjects in the fluticasone furoate/vilanterol group than the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			measurements, and exacerbations	tiotropium group demonstrated an onset of effect within the first five minutes of dosing (36% vs 23%, respectively). The percentage of rescue-free 24-hour periods was increased in the fluticasone furoate/vilanterol group compared with the tiotropium group during weeks 1 through 12 (LS mean change difference of 9.1%; 95% CI, 4.0 to 14.2). SGRQ-C scores and CAT measures improved from baseline in both treatment groups with no statically significant difference between groups. There was no clinically significant difference between treatment groups in the mean change from baseline for pulse rate, heart rate, or QTc intervals. Fewer patients in the fluticasone furoate/vilanterol group (2%) experienced a COPD exacerbation than in the tiotropium group (4%).
Saito et al.[71] (2015) Tiotropium 18 µg inhaled QD vs fluticasone propionate and salmeterol 250/50 µg inhaled BID plus tiotropium 18 µg inhaled QD vs fluticasone propionate and salmeterol 250/50 µg inhaled BID	DB, DD, MC, RCT, XO Japanese patients 40 to 80 years of age with a diagnosis of COPD, >10 pack year smoking history, post-bronchodilator FEV_1 30 to 75% of predicted, post bronchodilator FEV_1 to FVC ratio <70%, and mMRC dyspnea score ≥1.	N=53 16 weeks Patients spent four weeks in each treatment group with two weeks of washout in between	Primary: Post-morning dose specific airway conductance (sGAW) $AUC_{0–4h}$ on day 28 Secondary: Spirometry measures, rescue medication use, and adverse events	Primary: A statically significant improvement in post-morning dose sGAW $AUC_{0–4h}$ on day 28 was seen in the fluticasone propionate/salmeterol plus tiotropium group compared to the two other treatment groups. The ratio of endpoint adjusted mean for the post morning dose sGAW $AUC_{0–4h}$ on day 28 in the fluticasone propionate/salmeterol plus tiotropium group was 1.071 (SE=0.0263, 97.5% CI, 1.009 to 1.136; P=0.011 compared to the tiotropium group and 1.068 (SE=0.0261, 97.5% CI, 1.007 to 1.133; P=0.013) compared to the fluticasone propionate/salmeterol group. Secondary: On day 28, fluticasone propionate/salmeterol plus tiotropium provided significantly greater improvements in trough FEV_1 and post dose FEV_1 compared to the two other treatment groups. Differences in rescue medication use was not statically significant between treatment groups. Adverse events were reported by 33% of patients in the fluticasone propionate/salmeterol plus tiotropium group, 22% of patients in the fluticasone propionate/salmeterol and 16% of patients in the tiotropium

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group.
Rabe et al.[72] (2008) Tiotropium 18 µg QD and formoterol 12 µg BID vs salmeterol 50 µg BID and fluticasone 500 µg BID	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <80% and FEV_1/FVC ≤70% predicted at visit 1, and pre bronchodilator FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 AUC 0-12h and peak FEV_1 Secondary: Peak FVC and FVC AUC 0-12; morning predose FEV1 and FVC	Primary: The FEV_1 $AUC_{0–12}$ mean difference was 78 mL higher in patients receiving tiotropium and formoterol compared to those receiving salmeterol and fluticasone (P=0.0006). The difference in peak FEV_1 was 103 mL in favor of tiotropium and formoterol (P=0.0001). Secondary: The 12-h FVC profile and peak FVC were significantly higher with tiotropium and formoterol compared to salmeterol and fluticasone (P=0.0001). There was no significant difference in predose FEV_1, however the difference in predose FVC favored tiotropium and formoterol (P=0.05).
Brusasco et al.[73] (2003) Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, DD, PC, RCT Patients ≥40 years of age with COPD, a FEV_1 ≤65% of predicted and an FVC ≤70%	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: SGRQ, TDI, spirometry and adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared to placebo (P<0.01). The proportion of patients with at least one exacerbation was 32, 35, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (P>0.05). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant (P value not reported). The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared to 11.1 days in the salmeterol group and 10.9 days in the placebo group (P<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the six-month trial for the tiotropium, salmeterol and placebo groups, respectively. A significant difference was observed for tiotropium compared to placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared to the placebo group (P<0.001 and P<0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17). Tiotropium was statistically better than salmeterol in peak FEV_1 and AUC from 0 to three hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%; P value not reported).
Donohue et al.[74] (2002) Tiotropium 18 µg QD vs salmeterol 50 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable COPD, FEV_1 ≤60% of predicted normal and FEV_1/FVC ≤70%	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved significantly over placebo by 137 mL in the tiotropium group and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL; P<0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (P<0.01). Secondary: PEFR improved by 27.3, 21.4, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (P<0.001) and tiotropium was better than salmeterol in improving evening PEFR (P<0.05). At six months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference, 0.78 units; P<0.05). At six months, the mean improvement in SGRQ was -5.14 units for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				tiotropium (P<0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance (P value not reported).
Briggs et al.[75] (2005) Tiotropium 10 µg QD vs salmeterol 50 µg BID	DB, PG, RCT Patients with COPD	N=653 12 weeks	Primary: Lung function Secondary: Not reported	Primary: After 12 weeks, the average post-dose FEV_1 over 12 hours was significantly higher with *tiotropium* compared with *salmeterol* (167 vs 130 mL, respectively; P=0.03). Peak FEV_1 was significantly higher with *tiotropium* compared with *salmeterol* (262 vs 216 mL, respectively; P=0.01). The average FEV_1 responses from 0-6 h and 6-12 h were higher in the *tiotropium* group compared with *salmeterol* (P<0.05). Peak and average FVC were significantly higher with *tiotropium* compared with *salmeterol* (P<0.01). Morning pre-dose FEV_1 responses were not significantly different among the treatment groups. T*iotropium* demonstrated a significantly higher pre-dose FVC than *salmeterol* (P<0.05). Secondary: Not reported
van Noord et al.[76] (2010) Tiotropium 18 µg QD vs salmeterol 50 µg BID vs	DB, RCT, XO Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤60% predicted and FEV_1/FVC ≤70%	N=95 24 weeks	Primary: FEV_1, FVC, effects on dyspnea (TDI focal score), rescue albuterol use Secondary: Not reported	Primary: FEV_1 increased by 72 mL with tiotropium plus salmeterol QD compared to 97 mL with either monotherapy agent (P<0.0001). Treatment with tiotropium plus salmeterol BID provided comparable daytime bronchodilator effects (0-12h: 12mL; P=0.38) as tiotropium plus salmeterol QD, but significantly more bronchodilation during the night-time (12-24h: 73mL; P<0.0001). Clinically relevant improvements in TDI focal score were achieved with bronchodilator combinations including salmeterol QD or BID (2.56 and 2.71; P<0.005 vs monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium 18 µg QD and salmeterol 50 µg QD vs tiotropium 18 µg QD and salmeterol 50 µg BID				Symptom benefit of combination therapies was also reflected in less need for reliever medication. All treatments were well tolerated. Secondary: Not reported
Aaron et al.[77] (2007) Tiotropium 18 µg QD vs tiotropium 18 µg QD and salmeterol 50 µg BID vs tiotropium 18 µg QD plus fluticasone and salmeterol 500-50 µg BID (fixed-dose combination product)	DB, MC, PC, RCT Patients ≥35 years of age with ≥1 COPD exacerbation in last 12 months requiring systemic steroids or antibiotics; history of ≥10 pack-years of cigarette smoking; documented chronic airflow obstruction with FEV_1/FVC <0.70 and a postbronchodilator FEV_1 ≤65% of the predicted value	N=449 1 year	Primary: Proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics Secondary: Number of COPD exacerbations per patient-year; number of hospitalizations for COPD and all causes; changes in health-related quality of life, dyspnea, lung function	Primary: The proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics in the tiotropium and placebo group (62.8%) did not differ from the tiotropium and salmeterol group (64.8%; 95% CI, -12.8 to 8.8) or from the tiotropium plus fluticasone and salmeterol group (60.0%; 95% CI, -8.2 to 13.8). Secondary: COPD exacerbations did not significantly differ between the tiotropium and placebo and the other two treatment groups. Patients treated with tiotropium plus fluticasone and salmeterol had lower rates of severe exacerbations of COPD requiring hospitalization than did patients treated with tiotropium and placebo (P=0.01). Tiotropium and salmeterol did not statistically affect hospitalization rates compared with tiotropium and placebo. All-cause hospitalizations were reduced in patients treated with tiotropium plus fluticasone and salmeterol compared with patients treated with tiotropium and placebo (P=0.04). Treatment with tiotropium and salmeterol or tiotropium plus fluticasone and salmeterol improved health-related quality of life significantly more than did therapy with tiotropium and placebo. Dyspnea scores did not significantly differ among the treatment groups. Tiotropium plus fluticasone and salmeterol improved lung function compared with tiotropium and placebo (P=0.049). Tiotropium and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				salmeterol did not statistically improve lung function compared with tiotropium and placebo.
Welte et al.[78] (2009) Tiotropium 18 µg QD plus budesonide and formoterol 320-9 µg BID (fixed-dose combination product) vs tiotropium 18 µg QD	DB, PG, MC RCT Patients ≥40 years of age with COPD symptoms for ≥2 years, ≥1 COPD exacerbation in the previous 12 months requiring systemic steroids and/or antibiotics, smoking history of ≥10 pack-years, FEV_1 ≤50% predicted and FEV_1/FVC <70% predose	N=660 12 weeks	Primary: Change in pre-dose FEV_1 Secondary: Mean predose FVC and IC, mean postdose FEV_1, mean FVC at 5 and 60 minutes, IC at 60 minutes plus SGRQ	Primary: Treatment with budesonide and formoterol plus tiotropium significantly increased mean predose FEV_1 by 6% (65 mL) and mean postdose FEV_1 by 11% (123 and 131 mL at 5 and 60 min postdose, respectively) vs tiotropium monotherapy (all, P=0.001). Secondary: Mean change in predose FVC was 53 mL (P=0.021), 5 min postdose FVC was 157 mL (P=0.001), and 60 min postdose FVC was 160 mL (P=0.001). Mean change in predose IC was 64 mL (P=0.020) and 110 mL at 60 min postdose Over the study period, SGRQ improved 3.8 with budesonide and formoterol plus tiotropium compared to 1.5 with tiotropium alone (mean difference, -2.3; 95% CI, -4.23 to -0.32; P=0.023). Improvements in SGRQ of 4 were seen in 49.5 and 40.0% of patients in the budesonide and formoterol plus tiotropium and tiotropium alone, respectively (P=0.016). A similar proportion of patients in each arm had a deterioration in SGRQ more than -4 (27.6 and 29.7%, respectively). The number of severe exacerbations decreased by 62% (95% CI, 0.25 to 0.57; P=0.001).
Calverley et al.[79] (2018) DYNAGITO Tiotropium 5 µg once daily vs tiotropium-olodaterol 5 µg-5 µg once daily	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, FEV_1 ≤60% predicted, FEV_1/FVC <70%, and ≥1 moderate or severe exacerbation in the preceding	N=7,880 52 weeks	Primary: Rate of moderate and severe COPD exacerbations from the first dose of medication until one day after last drug administration Secondary: Time to first	Primary: The rate ratio for the rate of moderate and severe exacerbations was 0.93 (99% CI, 0.85 to 1.02) with tiotropium–olodaterol compared with tiotropium during the 52-week treatment period. The targeted significance level of 0.01 (i.e., necessitating a P<0.01) was not met, with a P-value of 0.0498. Secondary: The HR for time to first moderate or severe COPD exacerbation was 0.95 (99% CI, 0.87 to 1.03; P=0.12) with tiotropium–olodaterol versus tiotropium during the 52-week treatment period; the HR for time to first COPD exacerbation leading to hospitalization was 0.93 (95% CI, 0.82 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	year		moderate or severe COPD exacerbation during the treatment period, rate of exacerbations leading to hospitalization, time to first exacerbation leading to hospitalization, and time to all-cause mortality	1.06; P=0.28). For severe exacerbations, the rate ratio for tiotropium–olodaterol compared with tiotropium was 0.89 (95% CI, 0.78 to 1.02; P=0.090), and for exacerbations leading to hospitalization the rate ratio was 0.89 (95% CI, 0.76 to 1.03; P=0.13). Time to all-cause mortality was similar with tiotropium–olodaterol compared with tiotropium (HR, 0.88; 95% CI, 0.68 to 1.15).
Feldman et al.[80] (2016) Tiotropium 18 µg vs umeclidinium 62.5 µg	B, DD, MC, NI, RCT Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, FEV_1 ≤50% predicted and FEV_1/FVC <70% predose	N=1,017 12 weeks	Primary: FEV_1 at day 85 in the per-protocol population Secondary: FEV_1 in the intent-to-treat population, Transition Dyspnea Index (TDI), SGRQ, CAT score	Primary: The least squares mean change from baseline in trough FEV_1 was greater with umeclidinium than with tiotropium at day 85 in the per-protocol population (difference, 59 mL; 95% CI, 29 to 88; P<0.001). Similar results were observed in the analysis of trough FEV_1 at day 85 for the intent-to-treat population (53 mL; 95% CI, 25 to 81; P<0.001). Secondary: Umeclidinium resulted in a statistically significant difference in least squares mean change from baseline trough FEV_1 versus tiotropium at days 28, 56, and 84 (all P≤0.003) but not at day two. Umeclidinium also demonstrated a statistically significant difference in least square mean change from baseline trough FVC versus tiotropium at days 28, 56, 84, and 85 (all P≤0.016) but not at day two. Similar improvements were observed in TDI, SGRQ, and CAT score for umeclidinium and tiotropium. There were no differences between treatment groups in the least square mean change from baseline in rescue medication use over weeks one to 12 (0.0 puffs/day; 95% CI, −0.2 to 0.1), or in the median percentage of rescue-free days (0.0; 95% CI, 0.00 to 0.18).
Puhan et al.[81] (2009)	MA (35 trials) Patients with stable	N=26,786 ≥4 weeks	Primary: Comparison of treatments by	Primary: All regimens significantly reduced exacerbations compared to placebo: tiotropium (OR, 0.41; 95% CI, 0.64 to 0.80), ICS (OR, 0.78; 95% CI, 0.70

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tiotropium vs LABA monotherapy vs ICS monotherapy vs ICS and LABA combination therapy	COPD		reported COPD exacerbations Secondary: Comparison of treatments by reported COPD exacerbations in patients with FEV_1 ≤40% or FEV_1 >40% predicted	to 0.86), LABA (OR, 0.77; 95% CI, 0.64 to 0.84), and ICS and LABA (OR, 0.72; 95% CI, 0.64 to 0.80). Neither tiotropium nor combination therapy reduced exacerbations more than LABA monotherapy (OR, 1.02; 95% CI, 0.90 to 1.16 and OR, 0.93; 95% CI, 0.84 to 1.04, respectively). Combined treatment was not more effective than LABA or tiotropium monotherapy (OR, 0.93; 95% CI, 0.84 to 1.04 and OR, 1.02; 95% CI, 0.90 to 1.16, respectively). Secondary: In patients with FEV_1 ≤40% predicted, tiotropium, ICS, and ICS and LABA significantly reduced exacerbations compared to LABA monotherapy (OR, 0.83; 95% CI, 0.71 to 0.98; OR, 0.75; 95% CI, 0.57 to 1.00, and OR, 0.79; 95% CI, 0.67 to 0.93, respectively). In patients with FEV_1 >40% predicted, there was no difference in COPD exacerbations between treatments.
Triverdi et al.[82] (2014) Umeclidinium 125 µg vs umeclidinium 62.5 µg vs placebo	PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years, an established clinical history of COPD, FEV_1 ≤70% predicted and FEV_1/FVC ≤70%	N=206 12 weeks	Primary: Change from baseline in FEV_1 at day 85 Secondary: Weighted mean FEV_1 0 to 6 hours post dose on days 1, 28, and 84, transitional dyspnea index (TDI) score, rescue salbutamol use, SGRQ, safety	Primary: Change from baseline in FEV_1 was observed for umeclidinium 62.5 µg (127 mL; 95% CI, 52 to 202 mL) and 125 µg (152 mL; 95% CI, 76 to 229 mL) compared with placebo (P<0.001 for both). Secondary: Statistically significant (P<0.001) improvements were observed in LSM change from baseline in 0 to 6-hour weighted mean FEV_1 for both umeclidinium groups compared with placebo. The umeclidinium 62.5 and 125 µg treatment groups exhibited an LSM TDI focal score of 0.7 and 1.0 units, respectively, which is approximate to the clinically meaningful improvement 1 unit, whereas the placebo group had an LSM TDI focal score of -0.3, reflecting a worsening compared to baseline. The differences in rescue-treatment use from placebo were statistically significant for 62.5 µg (mean -0.7 puffs per day (95% CI, -1.3 to -0.1),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.025), but not 125 µg (mean -0.6 puffs per day (95% CI, -1.2 to 0.0), P=0.069). On day 84, the LSM change from baseline in SGRQ total score was -6.12 (125 µg), -3.14 (62.5 µg) and +4.75 (placebo). Overall incidence of adverse events was similar across treatment groups (62.5 µg, 39%; 125 µg, 41%; and placebo, 35%).
Donohue et al.[83] (2014) Umeclidinium 125 µg vs umeclidinium-vilanterol 125-25 µg vs placebo	DB, MC, PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years and an established clinical history of COPD	N=562 52 weeks	Primary: Safety, trough FEV_1, trough FVC Secondary: Not reported	Primary: The incidence of on-treatment adverse events (AEs), serious AEs (SAEs) and drug-related AEs was similar across active treatment groups and placebo. Greater mean changes from baseline in trough FEV_1 and FVC were demonstrated for umeclidinium-vilanterol and umeclidinium compared with placebo at all visits. At 12 months, umeclidinium-vilanterol and umeclidinium had improved trough FEV_1 in comparison with placebo by 0.231 L (95% CI, 0.153 to 0.310) and 0.178 L (95% CI, 0.098 to 0.258), respectively, and trough FVC by 0.252 L (95% CI, 0.135 to 0.368) and 0.194 L (95% CI, 0.076 to 0.312), respectively. There were fewer patients reporting COPD exacerbations with umeclidinium-vilanterol and umeclidinium (13 and 15%) compared with placebo (24%). Secondary: Not reported
Ismaila et al.[84] (2015) Tiotropium 18 µg QD vs newer agents (aclidinium 400 µg BID,	MA (24 trials) Adults with COPD	N=21,311 Variable duration	Primary: Change from baseline in trough FEV_1 to week 12 Secondary: Change from baseline in trough FEV_1 to week 24, transitional dyspnea index	Primary: In total, 17 studies (11,935 patients) were included for the FEV_1 endpoint. The minimal clinically important difference for FEV_1 is 100 mL. All LAMAs investigated were more efficacious than placebo, with a mean change from baseline greater than the minimal clinically important difference. The mean change from baseline in trough FEV_1 was highest for umeclidinium, with a difference of 136.7 mL (95% credible interval, 104.20 to 169.20) from placebo and a >99% probability of being better than placebo. The probability of umeclidinium being a better treatment than tiotropium, aclidinium, or glycopyrronium was 90, 96, or 86%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
glycopyrronium 50 µg QD, and umeclidinium 62.5 µg QD)			(TDI) score, SGRQ, and rescue medication use	Secondary: In total, eleven studies (15,663 patients) were included for the FEV_1 endpoint at 24 weeks. Again, the mean change from baseline was greater than the minimal clinically important difference for all active agents. The highest change from baseline in trough FEV_1 was found with glycopyrronium, with a difference of 135.8 mL (95% credible interval, 123.10 to 148.30). Glycopyrronium had a >99% chance of being better than tiotropium, which had the next highest difference in change from baseline trough FEV_1. The newest agent, umeclidinium, had a mean difference in change from baseline of 115.0 mL compared with placebo (95% credible interval, 74.51 to 155.30), with >99% probability of being better than placebo. Umeclidinium was comparable to other LAMAs for this endpoint, with only a 66, 33, and 17% probability of being better than tiotropium, aclidinium, and glycopyrronium, respectively. The minimal clinically important difference for SGRQ score is four units. Relative to placebo, only umeclidinium and aclidinium mean scores were reduced by more than four units, although all agents had 99% probability of being better than placebo. The minimal clinically important difference for TDI score is one unit. Aclidinium, glycopyrronium, and umeclidinium had a mean difference in change from baseline in TDI score of ≥1.00. Only the mean change in TDI score for tiotropium did not reach the minimal clinically important difference. Glycopyrronium, tiotropium, and umeclidinium reduced rescue medication use to comparable extents, with mean changes of −0.41 (95% credible interval, −0.62 to −0.20), −0.52 (95 credible interval, −0.74 to −0.30), and −0.30 puffs/day (95% credible interval, −0.81 to 0.21), relative to placebo.
Exercise-Induced Bronchoconstriction				
Spooner et al.[85] (2003) Inhaled mast-cell stabilizers (cromolyn sodium or nedocromil sodium)	MA (24 trials) Patients ≥6 years of age with exercise-induced bronchoconstriction with a fall in FEV_1 of ≥10% after an	N=518 Variable duration	Primary: Pulmonary function Secondary: Complete protection from exercise-induced	Primary: On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 7.1%, compared to a 13.8% fall observed in the anticholinergic group (95% CI, 3.3 to 10.0). On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 11.2%, compared to a 4.3% fall observed in the β_2-adrenergic agonist group (95% CI, 4.5 to 9.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs short-acting β_2-agonist, anticholinergic agent, or short-acting β_2-adrenergic agonist in addition to inhaled mast-cell stabilizers	exercise challenge test		broncho-constriction, clinical protection, adverse events, symptom score or preference measure	Secondary: Mast cell stabilizers provided a greater number of patients with complete protection (73 vs 56%; 95% CI, 1.3 to 3.7) and clinical protection from exercise-induced bronchoconstriction, compared with anticholinergic agents (73 vs 52%; 95% CI, 1.1 to 6.4). Mast cell stabilizers provided a fewer number of patients with complete protection (66 vs 85%; 95% CI, 0.2 to 0.5) and clinical protection from exercise-induced bronchoconstriction, compared with β_2-adrenergic agonists (55 vs 77%; 95% CI, 0.2 to 0.8). Patients receiving a combination of a short-acting β_2-adrenergic agonist and a mast-cell stabilizer did not exhibit statistically significant difference in improvement of pulmonary function compared to patients on short-acting β_2-adrenergic agonist alone (5.3 and 3.5% fall, respectively; 95% CI, 0.2 to 1.4).
Safety				
Singh et al.[86] (2011) Any inhaled anticholinergics for treatment of COPD	MA (17 RCTs) Patients receiving inhaled anticholinergics with more than 30 days of follow up, study participants with a diagnosis of COPD of any severity, an inhaled anticholinergic as the intervention drug vs a control, and reported data on the incidence of serious cardiovascular adverse events,	N=14,783 6 to 26 weeks	Primary: Composite of cardiovascular death, MI, or stroke Secondary: All-cause mortality	Primary: In a MA of 17 trials of 14,783 participants, cardiovascular death, MI, or stroke occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR, 1.58; 95% CI, 1.21 to 2.06; P<0.001). Among the individual components of the composite primary endpoint, inhaled anticholinergics significantly increased the risk of MI (1.2 vs 0.8% for control; RR, 1.53; 95% CI, 1.05 to 2.23; P=0.03) and cardiovascular death (0.9 vs 0.5% for control; RR, 1.80; 95% CI, 1.17 to 2.77; P=0.008), but did not significantly increase the risk of stroke (0.5 vs 0.4% for control; RR, 1.46; 95% CI, 0.81 to 2.62; P=0.20). Secondary: Inhaled anticholinergics did not significantly increase the risk of all-cause mortality (2.0 vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	including MI, stroke, or cardiovascular death			
Ogale et al.[87] (2010) Ipratropium exposure vs no ipratropium exposure	Cohort Veterans with a new diagnosis of COPD	N=82,717 6 years	Primary: Death or hospitalization from cardiovascular events during the period of interest (acute coronary syndrome, heart failure, or cardiac dysrhythmia) Secondary: Not reported	Primary: Forty percent of the cohort received no COPD medication during the study. More than 44% were exposed to anticholinergics at some time during the study period. A total of 329,255 prescriptions were dispensed for anticholinergic agents. Only 78 were for tiotropium, while the remaining prescriptions were for ipratropium alone by metered-dose inhaler (55%) or nebulization (7%), or ipratropium in a fixed-dose combination with albuterol (38%). During the total follow-up period of 274,025 patient-years, there were 6,234 cardiovascular events, for a rate of 2.2 cardiovascular events per 100 patient-years. Nearly 75% of the patients followed had at least one cardiovascular risk factor at study entry. There were 6,234 cardiovascular events (44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia). Compared with subjects not exposed to ipratropium within the past year, any exposure to ipratropium within the past six months was associated with an increased risk of cardiovascular event: ≤4 and ≥4 30-day equivalents (HR, 1.40; 95% CI, 1.30 to 1.51 and HR, 1.23; 95% CI, 1.13 to 1.36, respectively). Overall, exposure to anticholinergics was associated with a 29% higher risk of cardiovascular events relative to no exposure in the past year. Among subjects who received anticholinergics more than six months prior, there did not appear to be an elevated risk of a cardiovascular event. Effect modification by the presence of cardiovascular disease at baseline was statistically significant (P=0.01). Secondary: Not reported
Lee et al.[88] (2009)	Cohort Veterans ≥45 years	N=42,090 Death, no	Primary: Difference in all-cause mortality,	Primary: Treatment with tiotropium+ICS+LABA was associated with a 40% reduction in death compared with ICS+LABA (95% CI, 0.45 to 0.79).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tiotropium-containing regimens vs non-tiotropium combination regimens	of age with COPD who were switched to regimens containing tiotropium	prescription refill for 180 days, or 547 days from index date, whichever occurred first	COPD exacerbations, COPD hospitalizations Secondary: Not reported	Treatment with tiotropium+ICS+LABA was associated with a 16% reduction of COPD exacerbations compared with other regimens (95% CI, 0.73 to 0.97). There was no significant difference in exacerbations with tiotropium+ICS+LABA compared with ICS+LABA (HR, 1.03; 95% CI, 0.88 to 1.21). Treatment with tiotropium+ICS+LABA was associated with a 22% reduction of COPD hospitalizations compared with other regimens (95% CI 0.62 to 0.98). There was no significant difference in hospitalizations with tiotropium+ICS+LABA compared with ICS+LABA (HR, 1.15; 95% CI, 0.90 to 1.46). Other three drug combination regimens that included tiotropium and the four drug combination regimens that included tiotropium+ICS+LABA+ ipratropium were associated with increased mortality risk (HR, 1.38; 95% CI, 1.06 to 1.81 and HR, 1.36; 95% CI, 1.05 to 1.76, respectively). Secondary: Not reported
Celli et al.[89] (2009) UPLIFT Tiotropium 18 µg QD vs placebo	Post-hoc analysis Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, postbronchodilator FEV_1 ≤70% predicted and FEV_1 ≤70% of the FVC	N=5,993 4 years	Primary: Mortality Secondary: Mortality rates adjusted by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications	Primary: The total number of deaths from any cause (on-treatment) was 411 (13.6%) in the placebo group and 381 (12.8%) in the tiotropium group (HR, 0.84; 95% CI, 0.73 to 0.97; P=0.016). For the full four year, protocol-defined treatment period (1,440 days), there were 921 deaths. Mortality was significantly lower in patients randomized to tiotropium compared with placebo (HR, 0.87; 95% CI, 0.76 to 0.99; P=0.034). For the period of four years plus 30 days (1,470 days), there were 941 deaths, with a lower risk of death in the tiotropium group (HR, 0.89; 95% CI, 0.79 to 1.02; P=0.086). Between Days 1,440 and 1,470, there were four deaths in the placebo group and 16 deaths in the tiotropium group. Secondary: Adjustment by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications subgroups did not alter the results of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				analysis. The most common causes of death were lower respiratory events, cancer, general disorders, and cardiac disorders. The HRs for lower respiratory and cardiac mortality during treatment were 0.86 (95% CI, 0.68 to 1.09) and 0.86 (95% CI, 0.75 to 0.99), respectively.
Singh et al.[90] (2008) Tiotropium 5 to 10 µg vs placebo	MA (5 RCTs) Patients using tiotropium solution using a mist inhaler (Respimat® Soft Mist Inhaler) vs placebo for COPD that evaluated mortality as an outcome and had a trial duration of more than 30 days	N=6,522 Up to 52 weeks	Primary: Mortality from any cause Secondary: Deaths from cardiovascular causes (MI, stroke, cardiac death, and sudden death)	Primary: The tiotropium mist inhaler was associated with a significantly increased risk of mortality compared to placebo (RR, 1.52; 95% CI, 1.06 to 2.16; P=0.02). Secondary: Although the numbers for cardiovascular death were low, tiotropium was associated with a significantly increased RR in the five trials evaluating this outcome (RR, 2.05; 95% CI, 1.06 to 3.99; P=0.03).
Celli et al.[91] (2010) Tiotropium 18 µg QD vs placebo	MA (30 trials) Patients ≥40 years of age with COPD and smoking history of ≥10 pack-years, and spirometric confirmation of airflow limitation including an FEV_1 ≤70% of FVC	N=19,545 ≥4 weeks	Primary: All-cause mortality and selected cardiovascular events (composite of cardiovascular deaths, nonfatal MI, nonfatal stroke, and the terms sudden death, sudden cardiac death, and cardiac death) Secondary: Not reported	Primary: For all-cause mortality, the incidence rate was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years (RR, 0.88; 95% CI, 0.77 to 0.999). The incidence rate for the cardiovascular endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR, 0.83; 95% CI 0.71 to 0.98). The incidence rate for cardiovascular mortality (excluding nonfatal MI and stroke) was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years (RR, 0.77; 95% CI 0.60 to 0.98). The RRs of total MI, cardiac failure, and stroke were 0.78 (95% CI, 0.59 to 1.02), 0.82 (95% CI, 0.69 to 0.98), and 1.03 (95% CI, 0.79 to 1.35), respectively. Secondary: Not reported
Lee et al.[92]	Nested case-control	N=145,020	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Exposure to ICS, ipratropium, LABA, theophylline, and short-acting β_2-agonist	Patients treated in the United States Veterans Health Administration health care system	Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABA (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Barr et al.[93] (2005) Tiotropium vs placebo, ipratropium, LABA	MA (9 RCTs) Patients diagnosed with COPD, whose disease was stable	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations, mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use and adverse events	Primary: Reduced exacerbations were seen with tiotropium compared to placebo (OR, 0.75; 95% CI, 0.66 to 0.85) and compared to ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92). Hospitalizations for COPD exacerbations were reduced with tiotropium compared to placebo (OR, 0.65; 95% CI, 0.50 to 0.85) and compared to ipratropium or salmeterol but these differences were not statistically significant (OR, 0.59; 95% CI, 0.32 to 1.09 and OR, 0.59; 95% CI, 0.29 to 1.23). Cumulative all-cause mortality was 1.5% in the control groups and there were no statistically significant differences between any of the treatment groups over the duration of the trials (P value not reported). Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 from baseline that was statistically significant compared to the placebo group (140 mL; 95% CI, 118 to 162), the ipratropium group (150 mL; 95% CI, 106 to 193) and the salmeterol group (40 mL; 95% CI, 12 to 68). In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to the placebo group (278 mL; 95% CI, 208 to 348), the ipratropium group (210 mL; 95% CI, 112 to 308), and the salmeterol group (90 mL; 95% CI, 35 to 145). In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to the placebo group (21 mL; 95% CI, 15 to 28) and the ipratropium group (16 mL; 95% CI, 7 to 25). There was no difference between the tiotropium and salmeterol treatment groups (0 mL; 95% CI, -8 to 9). In the tiotropium group, dry mouth was significantly increased compared to the placebo group (OR, 5.4; 95% CI, 3.3 to 8.8), the ipratropium group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(OR, 2.1; 95% CI, 1.05 to 4.2) and the salmeterol group (OR, 5.1; 95% CI, 2.2 to 12.0).
Rodrigo et al.[94] (2009) Tiotropium vs placebo, LABA, or ICS and LABA	MA (19 trials) Patients >35 years of age with stable COPD	N=18,111 ≥4weeks	Primary: Major cardiovascular events (composite of nonfatal MI, stroke, and cardiovascular death), cardiovascular mortality (includes sudden death), nonfatal MI, and nonfatal stroke (includes transient ischemic attack) Secondary: All-cause mortality	Primary: There was no difference in the incidence of major cardiovascular events among the treatment groups (RR, 0.96; 95% CI, 0.82 to 1.12). There was no difference in cardiovascular deaths among the treatment groups (RR, 0.93; 95% CI, 0.73 to 1.20). There was no difference in nonfatal MI among the treatment groups (RR, 0.84; 95% CI, 0.6 to 1.09). There was no difference in nonfatal stroke among the treatment groups (RR, 1.04; 95% CI, 0.78 to 1.39). Secondary: Tiotropium did not significantly increase the risk of all-cause mortality (RR, 0.97; 95% CI, 0.86 to 1.09).
Dong et al.[95] (2013) Tiotropium vs LABA vs ICS vs LABA and ICS combination	MA (42 trials) Patients with COPD	N=52,516 ≥6 months	Primary: Mortality Secondary: Not reported	Primary: Results indicated that tiotropium Soft Mist Inhaler® was associated with an increased risk of overall death compared to placebo (OR, 1.51; 95% CI, 1.06 to 2.19), tiotropium Handihaler® (OR, 1.65; 95% CI, 1.13 to 2.43), LABA (OR, 1.63; 95% CI, 1.10 to 2.44), and LABA and ICS combination therapy (OR, 1.90; 95% CI, 1.28 to 2.86). The risk with tiotropium Soft Mist Inhaler® was more evident for cardiovascular death, severe COPD, and at higher daily doses. Among all treatments LABA and ICS combination therapy was associated with the lowest risk of death, while no excess risk was noted for tiotropium Handihaler® or LABA therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy vs placebo				
Baker et al.[96] (2009) Tiotropium vs ICS vs LABAs vs combination therapy	MA (43 trials) Patients with COPD	N=31,020 4 to 60 weeks	Primary: COPD exacerbations, all-cause mortality Secondary: Withdrawal from trial based on drug class	Primary: LABAs, tiotropium, ICSs, and combination ICS and LABA therapy each decreased the odds of having an exacerbation by 16, 31, 15, and 24%, respectively, compared to placebo. Tiotropium reduced the odds of having at least one exacerbation by 18% compared with LABAs and by 19% compared with ICSs alone. Compared to combination therapy, tiotropium reduced exacerbations by 9%. Only combination therapy was associated with a mortality benefit, showing a 29% reduction compared with placebo and a 25% reduction compared with LABAs alone. Compared to combination therapy, tiotropium use non-significantly increased mortality by 4%. Secondary: Each of the four drug classes was associated with a significant reduction in withdrawals (26 to 41%) compared with placebo. Both tiotropium and combination therapy significantly reduced patient withdrawals compared with LABAs or ICSs alone.
Karner et al.[97] (2011) Tiotropium and ICS/LABA vs tiotropium vs ICS/LABA	MA (3 RCTs) Patients 62 to 68 years with severity of COPD varied from moderate to very severe according to GOLD guideline definitions of COPD	N=1,051 Up to 52 weeks	Primary: All cause mortality, hospital admissions, exacerbations, pneumonia, SGRQ scores Secondary: Symptoms, FEV_1, non-fatal serious adverse events, adverse events and	Primary: There was no significant difference in mortality rates between patients receiving therapy with ICS/LABA plus tiotropium and tiotropium alone (OR, 1.88; 95% CI, 0.57 to 6.23; P=0.30). There were fewer patients admitted to the hospital who received ICS/LABA plus tiotropium (41/474) compared to the tiotropium plus placebo group (50/487); however, the difference between groups was not significant (OR, 0.84; 95% CI, 0.53 to 1.33). The number of patients admitted to hospital with exacerbations was higher in the tiotropium plus placebo group (38/487) compared to the ICS/LABA plus tiotropium group (25/ 474); however, this difference was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			withdrawals	significant (OR, 0.66; 95% CI, 0.39 to 1.13). Two studies examined the effect of ICS/LABA plus tiotropium on exacerbation rates compared to tiotropium alone. One study reported no difference in exacerbations between the treatment groups (OR, 0.89; 95% CI, 0.56 to 1.41), while the other study reported a significant reduction with the triple therapy compared to tiotropium monotherapy (OR, 0.36; 95% CI, 0.22 to 0.60). The risk of developing pneumonia was low, and there was no statistically significant difference between treatment with ICS/LABA plus tiotropium and tiotropium plus placebo (OR, 1.35; 95% CI, 0.31 to 5.99). Changes in SGRQ scores significantly favored ICS/LABA plus ipratropium treatment compared to ipratropium plus placebo after five months (P=0.002) and one year (P=0.01). Secondary: The addition of tiotropium to ICS/LABA significantly increased FEV_1 (difference, 0.06 L; 95% CI, 0.04 to 0.08 L), although this was below the threshold of 100 to 140 mL which is considered to be a clinically important increase. There were fewer patients suffering non-fatal serious adverse events in the tiotropium plus ICS/LABA group (12/504) compared to patients taking tiotropium plus placebo (20/517), although the difference was not statistically significant (OR, 0.60; 95% CI, 0.29 to 1.25). A higher number of patients suffered adverse events while treated with tiotropium plus ICS/LABA (140/504) compared to patients treated with tiotropium plus placebo (132/517), although the difference was not significant (OR, 1.12; 95% CI, 0.85 to 1.49). The difference between the number of patients who withdrew from the studies due to adverse events was not significantly different between patients taking tiotropium plus ICS/LABA and tiotropium plus placebo (OR, 0.92; 95% CI, 0.46 to 1.83).

Drug regimen abbreviations: QD=once daily, BID=twice daily, QID=four times daily
Study abbreviations: AC=active controlled, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, BDI=Baseline Dyspnea Index , BMI=body mass index, CI=confidence interval, COPD=chronic obstructive pulmonary disease, ECG=electrocardiogram, EELV=end-expiratory lung volume, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease , HR=hazard ratio, IC=inspiratory capacity, ICS=inhaled corticosteroids, LABA=long-acting beta agonists, LSM=least square mean, MACE= major adverse cardiovascular events, MDI=metered dose inhaler, MI=myocardial infarction, OR=odds ratio, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PR=pulmonary rehabilitation, RR=relative risk, SE=standard error, SEM=standard error of the mean, SF-36= 36-item short form health survey, SGRQ=St. George Respiratory Questionnaire, SVC=slow vital capacity, TDI=Transition Dyspnea Index , WMD=weighted mean difference

Additional Evidence

Dose Simplification
Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another. However, it should be noted that devices studied are only equally effective in patients who can use them appropriately. It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[98] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[75] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[99] Patient preference should be considered when selecting an inhalation delivery device. Barta et al. mailed a survey to 82 patients (most with chronic obstructive pulmonary disease [COPD]) using a home nebulizer treatment. It consisted of 29 questions covering topics of well-being, symptom control, self-confidence, dependency, time, and technical issues, side effects, and compliance. In the questionnaire, 98% of patients reported the benefits of using a nebulizer outweighed the disadvantages. The perceived advantages were the ability to control symptoms and be less dependent on health care providers, hospitals, and care givers.[102] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[98]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Inhaled Antimuscarinics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aclidinium	aerosol inhaler	Tudorza Pressair®	$$$$$	N/A
Glycopyrrolate	inhalation solution	Lonhala Magnair®	$$$$$	$$$
Ipratropium	aerosol inhaler, inhalation solution*	Atrovent HFA®	$$$$$	$
Revefenacin	inhalation solution	Yupelri®	$$$$$	N/A
Tiotropium	dry powder inhaler, solution inhaler	Spiriva Handihaler®, Spiriva Respimat®	$$$$$	N/A
Umeclidinium	dry powder inhaler	Incruse Ellipta®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

The inhaled antimuscarinics are approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-10] Tiotropium is also approved to reduce exacerbations in patients with COPD and for the maintenance treatment of asthma (Respimat® formulation only).[7-8] Tiotropium has a longer duration of action than ipratropium, which distinguishes tiotropium and ipratropium as long- and short-acting antimuscarinics, respectively.[2] Aclidinium, umeclidinium, and glycopyrrolate are more recently approved long-acting inhaled antimuscarinics, similar to tiotropium.[1-3,9] Lonhala Magnair® is a formulation of glycopyrrolate that is dosed twice-daily via nebulizer.[4] Yupelri® (revefenacin) was FDA-approved in November 2018 for the maintenance treatment of patients with COPD. It is administered once daily via nebulizer.[6] Ipratropium inhalation solution is the only product that is available in a generic formulation.

The 2021 Global Initiative for Asthma (GINA) includes recommendations published in 2019, prompted by concerns about the risks and consequences of the long-standing approach of initiating asthma treatment with short-acting β_2-agonists (SABA) alone. "For safety, GINA no longer recommends treatment of asthma in adolescents and adults with SABA alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment."[16] Since gaining the indication for the treatment of asthma in 2015, tiotropium has been added to the GINA guidelines as step four add-on therapy for patients with a history of exacerbations.[15,16] In three clinical trials comparing Spiriva Respimat® to placebo, the primary endpoint of peak FEV_1 response was found to have a statistically significant greater improvement with Spiriva Respimat®.[19-21]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline was updated in 2022. Initiation of maintenance pharmacological therapy should be based on the individualized assessment of symptoms and exacerbation risk. Generally, a long-acting β_2 agonist (LABA) or long-acting antimuscarinic agent (LAMA) is recommended when beginning treatment. Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation.[12] Most trials have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[12] Therefore, the goal of treatment is to decrease symptoms and complications. Bronchodilators are central to the symptomatic management of COPD. Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[12,13] When selecting an inhaled antimuscarinic, a long-acting agent is preferred over a short-acting agent due to differences in efficacy.[12,13]

Clinical trials have demonstrated that the regular use of a short- or long-acting antimuscarinic improves health status.[27-81] Tiotropium has been shown to significantly reduce COPD exacerbations, improve spirometric indices, and lead to improvements in quality of life and symptom scales compared to treatment with ipratropium.[61,63] Similar results were observed in a meta-analysis of 16 trials comparing tiotropium, ipratropium, and long-acting β_2-agonist therapy.[63] In addition, tiotropium may provide a greater clinical benefit than long-acting β_2-agonists.[69,73-76,101] Treatment with aclidinium, a long-acting inhaled antimuscarinic, has demonstrated statistically significant improvements in pulmonary function, COPD symptoms, and quality of life in patients with COPD compared to placebo.[27-32] A trial comparing aclidinium to tiotropium found the effects of the medications to be

similar over six weeks of treatment.[33] Treatment with umeclidinium has also demonstrated statistically significant improvements in pulmonary function, COPD symptoms, and quality of life in patients with COPD compared to placebo.[82,83] One trial directly comparing tiotropium and umeclidinium found that the least squares mean change from baseline in trough FEV_1 was greater with umeclidinium than with tiotropium at day 85 in the per-protocol population (difference, 59 mL; 95% CI, 29 to 88; P<0.001).[80] A meta-analysis of 24 trials comparing the inhaled antimuscarinics demonstrated that all LAMAs investigated were more efficacious than placebo, and the mean change from baseline in trough FEV_1 was highest for umeclidinium.[84] Revefenacin has demonstrated statistically significant improvements in FEV_1 compared to placebo, and similar changes in FEV_1 to that of tiotropium.[47-49]

Several meta-analyses and observational studies have been conducted by independent investigators to assess the link between the use of inhaled antimuscarinics and cardiovascular events.[30,54,86,87,90,91,94] In 2008, the Food and Drug Administration (FDA) released several communications describing a potential increased risk of stroke, myocardial infarction, or death from cardiovascular causes with tiotropium.[17] However, the results of the UPLIFT trial did not support these findings.[51,89] In January 2010, the FDA completed its review and informed health care providers that the data do not support an association between the use of tiotropium and an increased risk for these serious adverse events.[18]

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another. However, it should be noted that devices studied are only equally effective in patients who can use them appropriately. When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[98]

Therefore, all brand short-acting inhaled antimuscarinics within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Aclidinium, glycopyrrolate, revefenacin, tiotropium, and umeclidinium offer significant clinical advantages in general use over short-acting inhaled antimuscarinics.

XI. Recommendations

No brand short-acting inhaled antimuscarinic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

At least one long-acting inhaled antimuscarinic is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting antimuscarinic is selected as a preferred agent.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Beta-Adrenergic Agonists
AHFS Class 121208
August 10, 2022

I. Overview

The respiratory beta-adrenergic agonists (β_2-agonists) are approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasm.[1-19] They stimulate β_2-receptors and relax airway smooth muscle, which leads to bronchodilation.

All of the β_2-agonists elicit a similar biologic response; however, they differ in their dosing requirements, pharmacokinetic parameters, and adverse events. Short-acting β_2-agonists include albuterol, ipratropium-albuterol, levalbuterol, metaproterenol, and terbutaline. These agents increase airflow within 30 minutes and the effects may last up to four to five hours. Short-acting β_2-agonists are the treatment of choice for relieving acute asthma symptoms; however, they are not recommended for scheduled daily use. Long-acting β_2-agonists (LABAs) include albuterol (extended-release tablets), arformoterol, formoterol, and salmeterol. They are administered twice daily for the maintenance treatment of bronchospasm associated with asthma and COPD. Additional once-daily LABAs have been approved, including olodaterol in 2014 and a umeclidinium-vilanterol combination inhaler in 2013.[1-19] In 2019 a new combination product containing aclidinium and formoterol was approved for the maintenance treatment of patients with COPD.[13] Combination products are available with aclidinium, glycopyrrolate, ipratropium, tiotropium, and umeclidinium, which are all anticholinergic agents.[1,2]

The respiratory beta-adrenergic agonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Albuterol (aerosol inhaler, immediate-release tablets, inhalation solution, sustained-release tablets, and syrup), ipratropium-albuterol (inhalation solution), levalbuterol (inhalation solution and aerosol inhaler), metaproterenol (syrup), and terbutaline (injection and tablets) are available in a generic formulation. There are currently no dry powder inhalers available generically. This class was last reviewed in May 2020.

Table 1. Respiratory Beta-Adrenergic Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Albuterol	aerosol inhaler*, dry powder inhaler, extended-release tablet*, inhalation solution*, syrup*, tablet*	ProAir Digihaler®, ProAir HFA®*, ProAir Respiclick®, Proventil HFA®*, Ventolin HFA®*	albuterol, ProAir HFA®‡
Arformoterol	inhalation solution	Brovana®*	arformoterol
Formoterol	inhalation solution	Perforomist®*	formoterol
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®*	levalbuterol, Xopenex HFA®*
Metaproterenol	syrup*	N/A	metaproterenol
Olodaterol	solution inhaler	Striverdi Respimat®	Striverdi Respimat®
Salmeterol	dry powder inhaler	Serevent Diskus®	Serevent Diskus®
Terbutaline	injection*, tablet*	N/A	terbutaline
Combination Products			
Aclidinium and formoterol	aerosol inhaler	Duaklir Pressair®	none
Glycopyrrolate and formoterol	aerosol inhaler	Bevespi®	none
Ipratropium and albuterol	inhalation solution*, solution inhaler	Combivent Respimat®	albuterol and ipratropium, Combivent Respimat®
Tiotropium and olodaterol	solution inhaler	Stiolto Respimat®	Stiolto Respimat®

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Umeclidinium and vilanterol	dry powder inhaler	Anoro Ellipta®	Anoro Ellipta®

*Generic is available in at least one dosage form or strength.
‡During the COVID-19 state of emergency, all albuterol inhalers were temporarily designated as preferred.
HFA=hydrofluorocarbon, N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory beta-adrenergic agonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Respiratory Beta-Adrenergic Agonists

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022)**[20]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, sputum production, history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease. • Spirometry is required to make the diagnosis; the presence of a post-bronchodilator Forced Expiratory Volume in one second (FEV_1)/ Forced Vital Capacity (FVC) ratio of <0.07 confirms the presence of persistent airflow limitation. • The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbation, hospital admissions, or death), in order to guide therapy. • Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer; these comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalizations independently. Prevention and maintenance therapy • Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. • The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present. • Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. • Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices. • Inhaler technique needs to be assessed regularly. • COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations. • Influenza vaccination decreases lower respiratory tract infections. • Pneumococcal vaccination decreases lower respiratory tract infections. • CDC recommends the Tdap vaccination (dTaP/dTPa) in COPD patients to protect against pertussis, tetanus and diphtheria, in those who were not vaccinated in adolescence and Zoster vaccine to protect against shingles for adults with COPD aged ≥50 years. • Pulmonary rehabilitation improves exercise capacity, symptoms and quality of life across all grades of COPD severity. • In patients with severe resting chronic hypoxemia, long-term oxygen therapy

Clinical Guidelines	Recommendations
	improves survival. • In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. Individual patient factors must be considered when evaluating the patient's need for supplemental oxygen. • In patients with severe chronic hypercapnia and a history of hospitalizations for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization. • In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial. • Palliative approached are effective in controlling symptoms in advanced COPD. <u>Pharmacologic therapy for stable COPD</u> • Bronchodilators o Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. o Regular and as-needed use of short-acting β_2-agonist (SABA) or short-acting antimuscarinic (SAMA) improves FEV_1 and symptoms. o Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms. o Long-acting β_2.agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) improve lung function, dyspnea, health status, and reduce exacerbation rates. o LAMAs have a greater effect on reducing exacerbations than LABAs and decrease hospitalizations. o Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy. o Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy. o Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance. o Theophylline exerts a small bronchodilator effect in stable COPD and that is associated with modest symptomatic benefits. • Anti-inflammatory therapy o Inhaled corticosteroids ▪ An inhaled corticosteroid (ICS) combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. ▪ Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease. ▪ Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations. o Oral glucocorticoids ▪ Long-term use of oral glucocorticoids has numerous side effects with no evidence of benefits. o Phosphodiesterase-4 (PDE4) inhibitors ▪ In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations, a PDE4 inhibitor improves lung function and reduces moderate to severe exacerbations and improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations.

Clinical Guidelines	Recommendations
	○ Antibiotics ▪ Long-term azithromycin and erythromycin therapy reduces exacerbations over one year. ▪ Treatment with azithromycin is associated with an increased incidence of bacterial resistance and hearing test impairments. ○ Mucoregulators and antioxidant agents ▪ Regular treatment with mucolytics such as erdosteine, carbocysteine, and N-acetylcysteine (NAC) reduces the risk of exacerbations in select populations. ○ Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy. ○ Leukotriene modifiers have not been adequately tested in COPD patients. ○ Intravenous augmentation therapy may slow down the progression of emphysema. ○ There is no conclusive evidence of a beneficial role of antitussives in patients with COPD. Vasodilators do not improve outcomes and may worsen oxygenation. <u>Management of stable COPD</u> • LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy. • Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. • Inhaled bronchodilators are recommended over oral bronchodilators. • Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable. • Long-term monotherapy with ICS is not recommended. • Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators. • Long-term therapy with oral corticosteroids is not recommended. • In patients with severe to very severe airflow limitation, chronic bronchitis, and exacerbations the addition of a PDE4 inhibitor to a treatment with long-acting bronchodilators with/without ICS can be considered. • Preferentially but not only in former smokers with exacerbations despite appropriate therapy, macrolides (in particular azithromycin) can be considered. • Statin therapy is not recommended for prevention of exacerbations. • Antioxidant mucolytics are recommended only in select patients. • Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. • Antitussives cannot be recommended. • Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD. • Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease. <u>Management of exacerbations</u> • The most common causes of an exacerbation are viral respiratory tract infections. • The goal of treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events. • SABA with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation. • Maintenance therapy with long-acting bronchodilators should be initiated as soon

Clinical Guidelines	Recommendations
	as possible before hospital discharge. • Systemic corticosteroids can improve lung function (FEV_1), oxygenation, and shorten recovery time and length of hospital stay. Duration of therapy should not be more than five to seven days. • Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be five to seven days. • Methylxanthines are not recommended due to increased side effect profiles.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)[21]**	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
Department of Veterans Affairs/ Department of Defense:	Diagnosis and classification • Post-bronchodilator spirometry is suggested to confirm clinical diagnosis of COPD. • There is insufficient evidence to recommend for or against any specific clinical

Clinical Guidelines	Recommendations
Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2021)[22]	criteria to inform decision-making regarding advancing pharmacologic therapy for COPD. Risk reduction and first-line therapy • Smoking cessation is recommended for prevention and risk reduction of COPD. • Routine vaccination for influenza and pneumococcal pneumonia is suggested for prevention and risk reduction of COPD exacerbations. • LAMA is recommended as first-line therapy in patients with symptomatic COPD. • Inhaled LABA should not be offered as first-line therapy in patients with symptomatic COPD, unless a LAMA is not tolerated or is contraindicated. • ICS should not be offered to patients with symptomatic COPD as a first-line therapy. • For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a LAMA, adding a LABA to LAMA therapy is suggested. • If choosing dual therapy, offering LABA with ICS for patients with COPD is not recommended. • In patients with COPD who are on combination therapy with a LAMA/LABA and continue to have COPD exacerbations, adding an ICS as a third medication is suggested. • There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy. • Consider withdrawal of ICS in patients with COPD without moderate to severe exacerbations in the last two years. • There is insufficient evidence to recommend for or against the use of NAC preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). • There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not). • Providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia or chronic stable resting moderate hypoxemia with signs of tissue hypoxia is recommended. • Routinely offering ambulatory long-term supplemental oxygen is not suggested for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. • In patients with COPD, starting or continuing cardio-selective beta-blockers is suggested only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction). • Supported self-management program and telehealth support should be offered.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2021)[23]**	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences.

Clinical Guidelines	Recommendations
	• For population-level decisions about asthma treatment, the 'preferred option' represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk. • For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues. <u>Medications and strategies for symptom control and risk reduction</u> • For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone. • This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms. • Choice of reliever o Low dose ICS-formoterol is the preferred approach recommended by this guideline. o SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy. • Mild asthma o Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death. o In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. • Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique o Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities. ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium. ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age. ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA. ▪ For children, try other controller options at the same step before stepping up. ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. • Stepping down to find the minimum effective dose o Consider step down once good asthma control has been achieved and maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma.

Clinical Guidelines	Recommendations

	• For all patients with asthma
	  ○ Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect.
	  ○ Encourage adherence with controller medication, even when symptoms are infrequent.
	  ○ Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations.
	  ○ For patients with one or more risk factors for exacerbations:
	  ▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients.
	  ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function).
	  ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies).
	• Difficult-to-treat and severe asthma
	  ○ Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics.
	
	<u>Categories of asthma medications</u>
	• *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise.
	• *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
	• *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.
	
	<u>Initial controller treatment</u>
	• For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.
	
	<u>Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u>
	• Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
	• If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>

Incorrect inhaler technique.
Poor adherence.
Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
Comorbidities that may contribute to respiratory symptoms and poor quality of life.
Incorrect diagnosis.

<table>
<tr><th colspan="6">Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)</th></tr>
<tr><td rowspan="2">Controller and preferred reliever (Track 1)</td><td colspan="3">Steps 1 to 2
As-needed low dose ICS-formoterol</td><td>Step 3
Low dose maintenance ICS-formoterol</td><td>Step 4
Medium dose maintenance ICS-formoterol</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol</td></tr>
<tr><td colspan="5">Reliever: as-needed low-dose ICS-formoterol</td></tr>
<tr><td rowspan="2">Controller and alternative reliever (Track 2)</td><td>Step 1
Take ICS whenever SABA taken</td><td>Step 2
Low dose maintenance ICS</td><td>Step 3
Low dose maintenance ICS-LABA</td><td>Step 4
Medium/high dose maintenance ICS-LABA</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA</td></tr>
<tr><td colspan="5">Reliever: as-needed SABA</td></tr>
</table>

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

<table>
<tr><th colspan="6">Personalized management to control symptoms and minimize future risk (six to 11 years of age)</th></tr>
<tr><th></th><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td>Preferred controller</td><td>Low dose ICS taken when SABA is taken</td><td>Daily low dose ICS</td><td>Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy</td><td>Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy Refer for expert advice</td><td>Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)</td></tr>
<tr><td>Other controller options</td><td>Consider daily low dose ICS</td><td>Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken</td><td>Low dose ICS+LTRA</td><td>Add tiotropium, or add LTRA</td><td>Add-on anti-IL5, or add-on low dose OCS, but consider side effects</td></tr>
<tr><td>Reliever</td><td colspan="5">As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)</td></tr>
</table>

<u>Management of worsening asthma and exacerbations</u>

Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize

</td></tr>
</table>

Clinical Guidelines	Recommendations
	and respond to worsening asthma. o The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment. o Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately. o The action plan can be based on changes in symptoms or (in adults) peak expiratory flow. • For patients presenting with an exacerbation to a primary care or acute care facility: o Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. o Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given. o Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be reviewed after one hour. o Ipratropium bromide treatment is recommended only for severe exacerbations. o Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment. o Chest X-ray or prescribing antibiotics is not routinely recommended. o Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. o Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use. • Arrange early follow-up after any exacerbation, regardless of where it was managed. o Review the patient's symptom control and risk factors for further exacerbations. o Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks. o Provide a written asthma action plan and advice about avoiding exacerbation triggers. o Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> • The goals of asthma management in young children are similar to those in older patients: o To achieve good control of symptoms and maintain normal activity levels. o To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects. • Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective. • A trial of controller therapy should be given if the symptom pattern suggests

Clinical Guidelines	Recommendations

asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.

- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Personalized management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

<u>Management of worsening asthma and exacerbations in children five and younger</u>

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - There is no compelling evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%).
  - Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  - Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days

Clinical Guidelines	Recommendations
	for children attending an emergency department or admitted to hospital, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma management.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2019)**[24]	<u>Pharmacological management</u> • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%. • Intermittent reliever therapy: o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. o For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. o Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years of age with asthma. o ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: o In adults, the first choice add-on therapy to an ICS is a LABA, which should be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is

Clinical Guidelines	Recommendations
	not taken without ICS, and to improve inhaler adherence. o In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: o If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: o All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. o If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed) ▪ Add tiotropium (adults) ▪ Add a theophylline. o If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). o Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored. o Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. o Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. o The use of immunotherapy is not recommended for the treatment of asthma in adults or children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory beta-adrenergic agonists are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity Respiratory Beta-Adrenergic Agonists[1-19]

Indication	Albuterol	Arformoterol	Formoterol	Levalbuterol	Metaproterenol	Olodaterol	Salmeterol	Terbutaline
Asthma								
Relief of bronchospasm in patients with asthma	✔ †‖							
Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	✔ ‡§			✔ †‡				
Treatment of asthma and prevention of bronchospasm as concomitant therapy with an ICS in patients with reversible obstructive airways disease, including patients with nocturnal symptoms							✔	
Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema					✔			✔
COPD								
Long-term, twice daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema		✔	✔				✔	
Long term, once-daily maintenance bronchodilator treatment of airflow obstruction in COPD patients, including chronic bronchitis and/or emphysema						✔		
Exercised-Induced Bronchospasm								
Prevention of exercise-induced bronchospasm	✔ ‡§						✔	

†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
COPD=chronic obstructive pulmonary disease, ICS=inhaled corticosteroid

Table 4. FDA-Approved Indications for the Combination Respiratory Beta-Adrenergic Agonists[1-19]

Indication	Aclidinium and formoterol	Glycopyrrolate and formoterol	Ipratropium and albuterol	Tiotropium and olodaterol	Umeclidinium and vilanterol
COPD					
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema				✔	✔
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔	✔			
Patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔ (Combivent Respimat®)		
Treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator			✔ (inhalation solution)		

COPD=chronic obstructive pulmonary disease.

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory beta-adrenergic agonists are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Respiratory Beta-Adrenergic Agonists[1-19]

Generic Name(s)	Onset (minutes)	Duration (hours)	Bio-availability (%)	Protein Binding (%)	Excretion* (%)	Half-Life (hours)
Single Entity Agents						
Albuterol	Oral: within 30 Inhalation: within 5	Oral: 6 to 12 Inhalation: 3 to 6	INH: <20 IR/ER: 100	10	Renal (76 to 100) Feces (<20)	ER: 9.3 HFA: 4.6 to 6.0 Neb: 5 Tab: 5.0 to 7.2 Syrup: 5.0 to 7.2
Arformoterol	<7	Not reported	Not reported	52 to 65	Renal (67) Feces (22)	26
Formoterol	Within 5	8 to 12	Not reported	31 to 64	DPI: Renal (59 to 62) Neb: Renal (1.1 to 1.7)	DPI: 10 Neb: 7
Levalbuterol	5 to 17	3 to 6	Not reported	Not reported	Not reported	4
Metaproterenol	30	4	40	Not reported	Not reported	Not reported
Olodaterol	Not reported	7.5	30	60	Renal (38) Feces (53)	45
Salmeterol	5 to 45	12	Not reported	96	Renal (25 to 60)	5.5
Terbutaline	30 to 45	4 to 8	10 to 50	Not	Renal (30 to 50)	3.4

				reported		
Combination Products						
Aclidinium and formoterol	Not reported	Not reported	Not reported	Aclidinium: Not reported F: 46 to 58	Aclidinium: Renal (54 to 65), Feces (20 to 33) F: Renal (62), Feces (24)	Aclidinium: 12 F: not reported
Glycopyrrolate and formoterol	Not reported	Not reported	Not reported	G: Not reported F: 46 to 58	G: Renal (85) F: Renal (62), Feces (24)	G: 11.8 F: 11.8
Ipratropium and albuterol	15 to 45	3 to 6	A: <20 I: 2 to 7	A: 10 I: 0 to 9	A: Renal (76 to 100) I: Renal (3.7 to 5.6)	A: 5 I: 1.6
Tiotropium and olodaterol	Not reported	Not reported	T: 33 O: 30	T: 72 O: 60	T: Renal (18.6) O: Renal (9), Feces (84)	T: 25 O: 45
Umeclidinium and vilanterol	27	Not reported	Not reported	U: 89 V: 94	U: Renal (<1), Feces (92) V: Renal (70), Feces (30)	U: 11 V: 11

*Generally based on IV data.

A=albuterol, ER=extended-release oral formulation, F=formoterol, G=glycopyrrolate, HFA=hydrofluoroalkane, I=ipratropium, , INH=inhalation, IR=immediate-release oral formulation, Neb=nebulizer, O=olodaterol, T=tiotropium, U=umeclidinium, V=vilanterol

V. Drug Interactions

Major drug interactions with the respiratory beta-adrenergic agonists are listed in Table 6.

Table 6. Major Drug Interactions with the Respiratory Beta-Adrenergic Agonists[2]

Generic Name(s)	Interaction	Mechanism
Albuterol, arformoterol, formoterol, levalbuterol, salmeterol, terbutaline	β-adrenergic blocking agents	Pharmacologic effects of beta-adrenergic agonists may be decreased by beta-adrenergic blockers. Untoward physiologic effects, characterized by bronchospasm, may occur.
Albuterol	Atomoxetine	Concurrent use of albuterol and atomoxetine may result in an increase in heart rate and blood pressure.
Albuterol, levalbuterol	Tricyclic antidepressants	Concurrent use of beta-adrenergic agonists and tricyclic antidepressants may result in an increased risk of cardiovascular system effects (e.g., tachycardia, blood pressure changes).
Formoterol	QT-interval prolonging agents	Concurrent use of formoterol and QT interval prolonging drugs may result in increased risk of QT-interval prolongation.
Levalbuterol	Epinephrine	Concurrent use of epinephrine and levalbuterol may result in increased risk of adverse cardiovascular effects.
Salmeterol	Drug impacting CYP3A	Concurrent use of salmeterol and strong CYP3A inhibitors may result in increased risk of cardiovascular adverse effects.
Vilanterol	Strong CYP3A4 inhibitors	Vilanterol is a substrate of CYP3A4. Caution should be exercised when considering coadministration with ketoconazole and other known strong CYP3A4 inhibitors

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory beta-adrenergic agonists are listed in Tables 7 to 9. The boxed warnings for the long-acting respiratory beta-adrenergic agonists are listed in Tables 10 and 11. A meta-analysis of all clinical trial data for the long-acting β_2-agonists (LABAs) was presented at an Food and Drug Administration (FDA) Advisory Committee meeting in December 2008.[25] The meta-analysis included data from 110 trials, which included 60,954 patients. Three major outcomes were evaluated, including asthma-related death, death or intubation, and hospitalization. There was a significant difference in asthma-related deaths with LABAs compared to non-LABA therapy. There was also a significant difference in the composite outcome (death, intubation, hospitalization) between LABA and non-LABA therapy. In a subgroup analysis, the risk was 3.63 (95% confidence interval [CI], 1.51 to 5.75) per 1,000 subjects with the LABAs compared to non-LABA therapy in patients who were not receiving an inhaled corticosteroid. In contrast, patients who received an inhaled corticosteroid did not have an increased risk with LABAs (0.25; 95% CI, -1.69 to 2.18). Based on the findings of this meta-analysis, the Advisory Committee voted unanimously that the benefits of salmeterol and formoterol did not outweigh the risks and recommended that the labeling requirements with the LABAs be enhanced. In May 2019 the boxed warnings were removed from arformoterol, formoterol, olodaterol, glycopyrrolate-formoterol, tiotropium-olodaterol, and umeclidinium-vilanterol, and warnings were added for serious asthma-related events. The warning states that use of LABAs as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.[1-19]

Table 7. Adverse Drug Events (%) Reported with the Single Entity Respiratory Beta-Adrenergic Agonists (Drugs A – I)[1-19]

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡
Cardiovascular					
Angina	✔	✔	<3	7	✔
Arrhythmias	✔	✔	✔	<2	✔
Chest pain/discomfort	<1	0.9 to 1.7	✔	7	1.9
Congestive heart failure	-	-	-	<2	-
Electrocardiogram abnormal	-	-	-	✔	-
Heart block	-	-	-	<2	-
Hypertension	✔	✔	✔	✔	✔
Hypotension	✔	✔	✔	✔	✔
Myocardial ischemia/infarction	✔	✔	✔	<2	-
Palpitations	5	-	-	✔	✔
Tachycardia	5	✔	3	✔	✔
Central Nervous System					
Anxiety	✔	✔	✔	-	-
Agitation	-	-	-	<2	-
Central nervous system stimulation	✔	✔	✔	✔	-
Cerebral infarct	-	-	-	<2	-
Circumoral paresthesia	-	-	-	<2	-
Dizziness	2	✔	3	<2	1.6

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡
Drowsiness	<1	-	-	-	-
Excitement	20	-	-	-	-
Fatigue	-	-	-	<2	✔
Headache	7	0.9 to 1.7	7	✔	✔
Hypokinesia	-	-	-	<2	-
Insomnia	2	-	-	<2	1.5
Irritable behavior	✔	✔	✔	-	-
Nervousness	20	-	7	<2	✔
Nightmares	✔	✔	✔	-	-
Paresthesia	-	-	-	<2	-
Restlessness	<1	✔	<1	-	-
Somnolence	2	-	-	<2	-
Seizure	✔	✔	✔	-	-
Tremor	20	✔	✔	<2	1.9
Vertigo	-	-	✔	-	-
Weakness	2	-	-	-	-
Dermatological					
Angioedema	✔	-	✔	-	-
Dry skin	-	-	-	<2	-
Flushing	<1	-	-	-	-
Herpes simplex/zoster	-	-	-	<2	-
Pruritus	-	-	-	-	1.5
Rash	✔	✔	✔	4	1.1
Skin discoloration	-	-	-	<2	-
Skin hypertrophy	-	-	-	<2	-
Urticaria	✔	0.9 to 1.7	✔	✔	-
Endocrine and Metabolic					
Diabetes	-	-	-	-	-
Hyperglycemia	✔	-	-	✔	✔
Hypokalemia	✔	✔	✔	<2	✔
Lactic acidosis	✔	✔	✔	-	✔
Gastrointestinal					
Constipation	-	-	-	<2	-
Diarrhea	✔	✔	✔	6	-
Dry mouth	✔	✔	✔	-	1.2
Dyspepsia	✔	✔	✔	-	-
Gastroenteritis	✔	0.9 to 3.4	✔	<2	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡
Nausea	2	0.9 to 1.7	-	-	-
Oral candidiasis	-	-	-	<2	-
Oral moniliasis	-	-	-	<2	-
Periodontal abscess	-	-	-	<2	-
Rectal hemorrhage/melena	-	-	-	<2	-
Taste changes	✔	✔	✔	-	-
Vomiting	-	-	7	-	-
Genitourinary					
Breast neoplasm	-	-	-	<2	-
Calcium crystalluria	-	-	-	<2	-
Cystitis	-	-	-	<2	-
Glycosuria	-	-	-	<2	-
Hematuria	-	-	-	<2	-
Kidney calculus	-	-	-	<2	-
Nocturia	-	-	-	<2	-
PSA increase	-	-	-	<2	-
Pyuria	-	-	-	<2	-
Urinary tract disorder	-	-	-	<2	-
Urine abnormality	-	-	-	<2	-
Urinary difficulty	<1	✔	<1	-	-
Urinary tract infection	-	-	✔	-	-
Musculoskeletal					
Arthralgia	✔	✔	✔	<2	-
Arthritis	-	-	-	<2	-
Back pain	-	-	-	-	4.2
Bone disorder	-	-	-	<2	-
Leg cramps	-	-	-	4	1.7
Muscle cramps	✔	✔	✔	<2	1.7
Pain	<1	-	3 to 5	8	-
Rheumatoid arthritis	-	-	-	<2	-
Tendinous contracture	-	-	-	<2	-
Respiratory					
Asthma exacerbation	✔	11 to 13	✔	-	✔
Bronchitis	-	0.9 to 1.7	-	✔	4.6
Bronchospasm	✔	✔	✔	-	-
Chest infection	-	-	-	-	2.7
Cough	✔	✔	5	-	-

Adverse Events	Albuterol*	Albuterol‡	Albuterol§	Arformoterol	Formoterol‡
Cold symptoms	-	3.4	-	-	-
Drying of oropharynx	✔	✔	✔	-	-
Dysphonia	-	-	-	<2	1
Dyspnea	-	-	✔	4	2.1
Epistaxis	✔	✔	✔	-	-
Hoarseness	✔	✔	✔	-	-
Increased sputum	-	-	-	-	1.5
Lung carcinoma	-	-	-	<2	-
Lymphadenopathy	-	0.9 to 2.6	-	-	-
Nasal congestion	-	1	-	-	-
Nasopharyngitis	-	-	-	-	-
Oral mucosal abnormality	-	-	-	<2	-
Oropharyngeal pain	-	-	-	-	-
Pharyngitis	✔	<1	14	-	3.5
Pulmonary edema	✔	✔	✔	-	-
Respiratory disorder	-	-	-	2	-
Rhinitis	✔	✔	5 to 16	-	-
Sinusitis	-	-	-	5	2.7
Skin/appendage infection	-	0 to 1.7	-	-	-
Throat irritation	✔	✔	1	-	-
Upper respiratory tract infection	-	-	21	-	7.4
Viral respiratory infection	✔	2.6	7	-	-
Voice alterations	-	-	-	<2	-
Other					
Anaphylactic reaction	✔	0.9 to 3.4	6	✔	-
Back pain	-	-	-	6	-
Blurred vision	-	-	-	<2	-
Edema	-	-	✔	3	-
Fever	-	-	6	-	2.2
Glossitis	✔	✔	✔	-	-
Glaucoma	-	-	-	<2	-
Influenza	-	-	3	-	-
Otitis media	✔	0.9 to 4.3	✔	-	-
Peripheral edema	-	-	-	-	-
Tonsillitis	-	-	-	-	1.2
Tongue ulceration	✔	✔	✔	-	-
Viral infection	-	-	-	-	17.2

✔ Percent not specified.

- Event not reported.
*Oral formulations.
‡Inhalation solution formulation.
§Aerosol formulation.

Table 8. Adverse Drug Events (%) Reported with the Single Entity Respiratory Beta-Adrenergic Agonists (Drugs L – T)[1-19]

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Cardiovascular						
Angina	-	-	✔	-	-	-
Arrhythmias	-	✔	✔	-	1 to 3	1.5
Chest pain	<2	-	<1	-	-	-
Electrocardiogram abnormal	<2	-	-	-	-	-
Hypertension	<2	<2	0.4	-	-	-
Hypotension	<2	-	-	-	-	-
Palpitations	-	-	3.8	-	✔	5
Syncope	<2	-	<1	-	✔	-
Tachycardia	2.7	✔	17.1	-	✔	3.5
Vasodilations	-	-	-	-	-	1
Central Nervous System						
Anxiety	2.7	-	-	-	1 to 3	1
Asthenia	3	-	-	-	-	-
Dizziness	1.4 to 2.7	2.7	2.4	2.3	4	3.5
Fatigue	-	-	<1	-	-	-
Hallucinations	-	-	-	-	-	<1
Headache	-	-	7	-	13 to 17	7.5
Hypertonia	-	-	-	-	-	<1
Hypesthesia of the hand	<2	-	-	-	-	-
Insomnia	<2	-	1.8	-	-	1.5
Migraine	2.7	-	-	-	-	-
Nervousness	2.8 to 9.6	✔	20.2	-	✔	35
Paresthesia	<2	-	-	-	1 to 3	<1
Sensory disturbances	-	-	<1	-	1 to 3	-
Somnolence	-	-	-	-	-	5.5
Sweating	<2	-	-	-	-	1
Tremor	6.8	✔	1 to 17	-	✔	15
Weakness	-	-	<1	-	-	-
Dermatological						
Angioedema	-	✔	-	-	✔	-
Contact dermatitis	-	-	-	-	1 to 3	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Diaphoresis	-	-	<1	-	-	-
Eczema	-	-	-	-	1 to 3	-
Hives	-	-	<1	-	-	-
Photodermatitis	-	-	-	-	1 to 2	-
Pruritus	-	-	2	-	-	-
Rash	7.5	✔	-	2.2	1 to 3	<1
Skin reaction	-	-	-	-	4	-
Urticaria	3	✔	-	-	3	-
Endocrine and Metabolic						
Hyperglycemia	-	-	-	-	1 to 3	-
Gastrointestinal						
Constipation	-	<2	-	-	-	-
Dental discomfort	-	-	-	-	1 to 3	-
Diarrhea	1.5 to 6.0	-	1.2	2.9	-	-
Dry mouth	<2	-	<1	-	-	1.5
Dyspepsia	1.4 to 2.7	-	-	-	-	-
Dyspeptic symptoms	-	-	-	-	1 to 3	-
Gastroenteritis	<2	<2	-	-	-	-
Gastrointestinal infections	-	-	-	-	1 to 3	-
Gastrointestinal distress	-	-	-	-	1 to 3	-
Hyposalivation	-	-	-	-	1 to 3	-
Nausea	<2	-	3.6	-	1 to 3	3
Oral candidiasis	-	-	-	-	1 to 3	-
Taste changes	-	-	<1	-	-	-
Vomiting	<2	10.5	<1	-	3	<1
Genitourinary						
Vaginal moniliasis	-	<2	-	-	-	-
Hematuria	-	<2	-	-	-	-
Urinary tract infection	-	-	-	2.5	-	-
Musculoskeletal						
Arthralgia	-	-	-	2.1	1 to 2	-
Articular rheumatism	-	-	-	-	1 to 2	-
Leg cramps	2.7	-	-	-	-	-
Muscle cramps	-	-	-	-	3	-
Muscle spasm	-	-	-	-	3	<1
Muscle stiffness	-	-	-	-	1 to 3	-
Muscle tightness	-	-	-	-	1 to 3	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Muscle rigidity	-	-	-	-	1 to 3	-
Musculoskeletal inflammation	-	-	-	-	1 to 3	-
Myalgia	1.5	<2	-	-	12	-
Pain	1.4 to 3.0	4	<1	3.5	1 to 3	-
Respiratory						
Asthma	9.0 to 9.1	9.4	2	-	3 to 4	-
Bronchitis	-	2.6	-	4.7	7	-
Bronchospasm	-	-	-	-	✔	-
Cough	1.4 to 4.1	-	<1	4.2	4	-
Dyspnea	-	✔	-	-	-	-
Epistaxis	-	<2	-	-	-	-
Influenza	-	-	-	-	5	-
Laryngeal irritation/swelling	-	-	<1	-	1 to 3	-
Laryngeal spasm	-	-	-	-	1 to 3	-
Lung Disorder	-	<2	-	-	-	-
Nasopharyngitis	-	-	-	11.3	-	-
Oral mucosal abnormality	-	-	-	-	1 to 3	-
Pharyngitis	3.0 to 10.4	6.6 to 7.9	-	-	6	-
Rhinitis	2.7 to 11.1	7.4	-	-	2	-
Sinus headache	-	-	-	-	1 to 3	-
Sinusitis	1.4 to 4.2	-	-	-	-	-
Upper respiratory tract infection	-	-	-	8.2	-	-
Viral respiratory infection	-	-	-	-	4	-
Wheezing	<2	-	-	-	-	-
Other						
Accidental injury	4.5 to 6.1	9.2	-	-	-	-
Acne	-	<2	-	-	-	-
Anaphylaxis	-	-	-	-	1 to 3	-
Conjunctivitis	-	<2	-	-	1 to 3	-
Cyst	-	<2	-	-	-	-
Chills	<2	-	<1	-	-	-
Chatty	-	-	<1	-	-	-
Clonus on flexed foot	-	-	<1	-	-	-
Dysmenorrhea	-	<2	-	-	-	-
Ear pain	-	<2	-	-	-	-
Ear signs	-	-	-	-	4	-
Edema	-	-	<1	-	1 to 3	-

Adverse Events	Levalbuterol‡	Levalbuterol§	Metaproterenol*	Olodaterol	Salmeterol	Terbutaline*
Eye itch	<2	-	-	-	-	-
Fever	3.0 to 9.1	-	<1	-	1 to 3	-
Flu syndrome	-	<2	<1	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	<1
Herpes Simplex	-	<2	-	-	-	-
Lymphadenopathy	3	-	-	-	-	-
Turbinate edema	1.4 to 2.8	-	-	-	-	-
Viral infection	6.9 to 12.3	<2	-	-	-	-

✔ Percent not specified.
- Event not reported.
*Oral formulations.
‡Inhalation solution formulation.
§Aerosol formulation.

Table 9. Adverse Drug Events (%) Reported with the Combination Respiratory Beta-Adrenergic Agonists[1-19]

Adverse Events	Aclidinium and formoterol	Glycopyrrolate and formoterol	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Tiotropium and olodaterol	Umeclidinium and vilanterol
Cardiovascular						
Arrhythmias	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	✔	-
Chest pain/discomfort	-	-	2.6	-	-	<1
ECG changes	-	✔	-	-	-	-
Hypertension	-	-	-	-	✔	-
Palpitations	-	-	✔	-	✔	-
Tachycardia	-	-	✔	-	✔	-
Central Nervous System						
Dizziness	1 to <3	-	-	-	✔	-
Drowsiness	-	-	✔	-	-	-
Headache	6	-	-	2 to 3	-	-
Insomnia	1 to <3	-	-	-	✔	-
Dermatological						
Flushing	-	-	✔	-	-	-
Pruritus	✔	-	<1	-	✔	<1
Rash	✔	✔	<1	-	✔	<1
Urticaria	✔	✔	<1	-	✔	-
Gastrointestinal						
Abdominal pain	-	-	1	1	-	<1
Constipation	-	-	✔	-	✔	1
Diarrhea	-	-	1.8	-	-	2

Adverse Events	Aclidinium and formoterol	Glycopyrrolate and formoterol	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Tiotropium and olodaterol	Umeclidinium and vilanterol
Dry mouth	1 to <3	-	-	-	✔	<1
Dyspepsia	-	-	1.3	-	-	<1
Gastroesophageal reflux disease	-	-	-	-	✔	-
Gingivitis	-	-	-	-	✔	-
Glossitis	-	-	-	-	✔	-
Nausea	-	-	1.4	-	-	-
Oropharyngeal candidiasis	-	-	-	-	✔	-
Sore throat	-	-	✔	-	-	-
Taste changes	-	-	✔	-	-	-
Vomiting	-	-	-	-	-	<1
Genitourinary						
Dysuria	-	-	-	-	✔	-
Urinary retention	-	✔	-	-	✔	-
Urinary tract infection	1 to <3	3	1.6	-	✔	-
Musculoskeletal						
Arthralgia	1 to <3	-	✔	-	✔	-
Back pain	4	-	✔	-	4	-
Leg cramps	-	-	1.4	-	-	-
Muscle spasms	1 to <3	-	1	1	-	<1
Pain	1 to <3	-	1.3	-	-	1
Respiratory						
Bronchitis	-	-	1.7	3	-	-
Bronchospasm	✔	✔	✔	-	✔	-
Chronic obstructive pulmonary disease exacerbation	-	-	✔	-	-	-
Cough	1 to <3	4	-	2 to 3	4	<1
Dyspnea	-	-	-	2	-	-
Epistaxis	-	-	-	-	✔	-
Lower respiratory tract infection	-	-	-	-	-	1
Lung disease	-	-	6.4	-	-	-
Nasopharyngitis	-	-	-	3 to 4	12	-
Oropharyngeal pain	1 to <3	-	-	-	-	-
Pharyngitis	-	-	4.4	-	✔	2
Pneumonia	-	-	1.3	-	-	-
Rhinitis	-	-	-	-	-	-
Sinusitis	1 to <3	-	✔	-	✔	1
Upper respiratory tract infection	9	-	✔	3 to 4	-	-

Adverse Events	Aclidinium and formoterol	Glycopyrrolate and formoterol	Ipratropium and Albuterol‡	Ipratropium and Albuterol*	Tiotropium and olodaterol	Umeclidinium and vilanterol
Voice alterations	-	-	✔	-	-	-
Wheezing	-	-	✔	-	-	-
Other						
Acute eye pain	-	-	✔	-	-	-
Anaphylaxis	✔	-	-	-	-	-
Angioedema	-	✔	-	-	✔	-
Blurred vision	-	-	✔	-	✔	-
Conjunctivitis	-	-	-	-	-	<1
Dehydration	-	-	-	-	✔	-
Exacerbation of diabetes mellitus	-	✔	-	-	-	-
Glaucoma	-	-	-	-	✔	-
Hyperglycemia	-	-	-	-	-	-
Hypersensitivity	✔	✔	-	-	✔	-
Hypokalemia	-	✔	-	-	-	-
Influenza	1 to <3	-	-	-	-	-
Ketoacidosis	-	✔	-	-	-	-
Tooth abscess	1 to <3	-	-	-	-	-
Worsening glaucoma	-	-	✔	-	-	-

✔ Percent not specified.
- Event not reported.
‡Inhalation solution formulation.
*Solution inhaler.

Table 10. Boxed Warning for Salmeterol[1]

WARNING
Long-acting beta-2 adrenergic agonists, such as salmeterol, increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol vs 3 deaths out of 13,179 patients on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from long-acting beta-2 adrenergic agonists. Because of this risk, use of salmeterol for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use salmeterol only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue salmeterol) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use salmeterol for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Children and adolescents: Available data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of asthma-related hospitalization in children and adolescents. For children and adolescents with asthma who require addition of a long-acting beta-2 adrenergic agonist to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a long-acting beta-2 adrenergic agonist is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be ensured, a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 adrenergic agonist is recommended.

Table 11. Boxed Warning for Terbutaline[1]

WARNING
Prolonged tocolysis: Terbutaline has not been approved and should not be used for acute or maintenance tocolysis. In particular, do not use terbutaline for maintenance tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline to pregnant women. In mothers, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.

VII. Dosing and Administration

The usual dosing regimens for the respiratory beta-adrenergic agonists are listed in Table 12.

Table 12. Usual Dosing Regimens for the Respiratory Beta-Adrenergic Agonists[1-19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Albuterol	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler, dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler, dry powder inhaler: ≥4 years of age: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily	Aerosol inhaler: 90 µg 108 µg Dry powder inhaler: 90 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Inhalation solution: 2.5 mg 3 to 4 times daily Syrup: 2 to 4 mg 3 to 4 times daily; maximum, 8 mg 4 times daily Tablet (IR): 2 to 4 mg 3 to 4 times daily Tablet (SR): 4 to 8 mg every 12 hours; maximum, 32 mg daily Exercise-induced bronchospasm: Aerosol inhaler, dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	Inhalation solution: 2 to 12 years of age: 0.63 to 1.25 mg 3 to 4 times daily; maximum, 2.5 mg 3 to 4 times daily Syrup: 2 to 5 years of age: 0.1 mg/kg of body weight 3 times daily; maximum, 4 mg 3 times daily; 6 to 14 years of age: 2 mg 3 to 4 times daily; maximum, 24 mg daily Tablet (IR): 6 to 12 years of age: 2 mg 3 to 4 times daily Tablet (SR): 6 to 12 years of age: 4 mg every 12 hours; maximum, 24 mg daily in divided doses Exercise-induced bronchospasm: Aerosol inhaler, dry powder inhaler: ≥4 years of age: 2 inhalations 15 to 30 minutes before exercise	Inhalation solution: 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/0.5 mL 2.5 mg/3 mL 5 mg/mL Syrup: 2 mg /5 mL Tablet (IR): 2 mg 4 mg Tablet (SR): 4 mg 8 mg
Arformoterol	COPD: Inhalation solution: 15 µg every 12 hours; maximum 2 doses per 24 hours	Safety and efficacy in children has not been established.	Inhalation solution: 15 µg/2 mL
Formoterol	COPD: Inhalation solution: 20 µg every 12 hours	Safety and efficacy in children has not been established.	Inhalation solution: 20 µg/2 mL
Levalbuterol	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 0.63 mg 3 times daily every 6 to 8 hours; maximum, 1.25 mg 3 times daily	Asthma, nocturnal asthma, reversible bronchospasm: Aerosol inhaler: ≥4 years of age: 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations daily Inhalation solution: 6 to 11 years of age: 0.31 mg 3 times daily; maximum, 0.63 mg 3 times daily	Aerosol inhaler: 45 µg Inhalation solution: 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/3 mL 1.25 mg/0.5 mL
Metaproterenol	Asthma, nocturnal asthma, reversible bronchospasm: Syrup: 2 teaspoonfuls 3 to 4 times daily; maximum, titrated to patient's response	Asthma, nocturnal asthma, reversible bronchospasm: Syrup: 6 to 9 years of age (<60 lb): 1 teaspoonful 3 to 4 times daily >9 years of age (>60 lb): 2 teaspoonfuls 3 to 4 times daily; maximum, titrated to	Syrup: 10 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		patient's response	
Olodaterol	COPD: Solution inhaler: 2 inhalations once daily	Safety and efficacy in children have not been established.	Solution inhaler: 2.5 µg
Salmeterol	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler: 1 inhalation (50 µg) 2 times daily COPD: Dry powder inhaler: 1 inhalation (50 µg) 2 times daily Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation (50 µg) at least 30 minutes before exercise	Asthma, nocturnal asthma, reversible bronchospasm: Dry powder inhaler (≥4 years of age): 1 inhalation (50 µg) 2 times daily Exercise-induced bronchospasm: Dry powder inhaler (≥4 years of age): 1 inhalation (50 µg) at least 30 minutes before exercise	Dry powder inhaler: 50 µg
Terbutaline	Asthma, nocturnal asthma, reversible bronchospasm: Tablet: 2.5 to 5 mg repeated every 6 hours (3 times daily); maximum, 15 mg daily	Asthma, nocturnal asthma, reversible bronchospasm: Tablet (12 to 15 years of age): 2.5 mg repeated every 6 hours (3 times daily); maximum, 7.5 mg daily	Injection: 1 mg/mL Tablet: 2.5 mg 5 mg
Combination Products			
Aclidinium and formoterol	COPD: Aerosol inhaler: one inhalation twice daily	Safety and efficacy in children has not been established.	Aerosol inhaler: 400-12 µg
Glycopyrrolate and formoterol	COPD: Aerosol inhaler: 2 inhalations twice daily	Safety and efficacy in children has not been established.	Aerosol inhaler: 9-4.8 µg
Ipratropium and albuterol	COPD: Inhalation solution: 1 vial four times daily; maximum, 6 vials daily Solution inhaler: one inhalation (20-100 µg) four times daily; maximum, six inhalations a day	Safety and efficacy in children has not been established.	Inhalation solution: 0.5-3 mg/3 mL Solution inhaler: 20-100 µg
Tiotropium and olodaterol	COPD: Solution inhaler: 2 inhalations once daily	Safety and efficacy in children has not been established.	Solution inhaler: 2.5-2.5 µg
Umeclidinium and vilanterol	COPD: Dry powder inhaler: 1 inhalation once daily	Safety and efficacy in children has not been established.	Dry powder inhaler: 62.5-25 µg

IR=immediate-release, SR=extended-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory beta-adrenergic agonists are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Respiratory Beta-Adrenergic Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Nelson et al.[26] (2006) SMART Salmeterol 42 µg BID vs placebo	DB, MC, OS, PC, PG, RCT Patients >12 years of age with a diagnosis of asthma and currently using asthma medications	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations	Primary: There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol (P<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary endpoints. For the primary and two of the secondary endpoints there were a statistically significant difference in African Americans receiving salmeterol compared to placebo (P<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; P=0.022).
Salpeter et al.[27] (2006) Long-acting beta-adrenergic agonists vs	MA Patients diagnosed with asthma	N=33,826 (19 trials) ≥3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma	Primary: Long-acting beta-adrenergic agonists (formoterol and salmeterol) resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9), and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3) when compared with placebo, with similar risks seen in adults and children.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			exacerbations, asthma-related deaths Secondary: Not reported	Not reported
Von Berg et al.[28] (1998) Salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients 6 to 15 years of age with a documented history of reversible airway obstruction requiring β-adrenergic agonist treatment for symptomatic control	N=426 12 months	Primary: Change from baseline in mean morning PEF Secondary: Percent of symptom-free nights and days, percent of nights and days with no rescue inhaler, and incidence of asthma exacerbations	Primary: Over the first six months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared with 171 minutes for placebo. (P<0.001). This significant improvement was maintained throughout the second 6 months of the study (P=0.03). Over the first six months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with salmeterol compared with 121 minutes for placebo. (P<0.001). This significant improvement was maintained throughout the second six months of the study (P=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the treatment groups. There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (P<0.05). During the 12-month treatment period there was no statistically significant difference between the treatment groups in the number of patients with asthma exacerbations (P=0.20).
LaForce et al.[29] (2017) Albuterol multidose dry powder inhaler 90	DB, PG, RCT Children four to 11 years of age with a documented diagnosis of asthma	N=184 Screening period (1 to 9 days), a 2-week, single-	Primary: Baseline-adjusted percent-predicted FEV_1 AUC_{0-6} after dosing over the 3-week treatment	Primary: The least squares mean difference in primary efficacy variable was 25.0%•hour in favor of albuterol versus placebo (95% CI, 16.1 to 33.9; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg (ProAir RespiClick®), two inhalations four times daily vs placebo	for ≥6 months and FEV_1 of 50 to 95% of predicted	blind run-in period, and a 3-week, DB treatment period	period Secondary: Peak expiratory flow, maximum percentage change from baseline in FEV_1	Patients who were treated with albuterol experienced a significant improvement in baseline-adjusted peak expiratory flow AUC_{0-6} compared with those who received placebo; the least squares mean difference was 76.3 L/min•hour in favor of albuterol versus placebo (95% CI, 47.8 to 104.9; P<0.001). The maximum percentage change from baseline in FEV_1 and peak expiratory flow within two hours of dosing was greater in patients treated with albuterol compared with those who received placebo over the 3-week treatment period, on treatment day one, and on treatment day 22 (P<0.001).
Casaburi et al.[30] (1991) Albuterol 5 mg via compressed air vs isoproterenol 5 mg via compressed air	RCT Individuals presenting for routine pulmonary function testing	N=180 Clinic visit	Primary: FEV_1 and FVC Secondary: Not reported	Primary: There was no statistical difference in FEV_1 or FVC at five and 10 minutes post-administration between the two groups. Secondary: Not reported
Carl et al.[31] (2003) Albuterol 2.5 mg via nebulization (every 20 minutes for 2 hours) vs levalbuterol 1.25 mg via nebulization (every 20 minutes for 2 hours)	DB, PRO, RCT Individuals 1 to 18 years of age with diagnosed with asthma presenting to the ED (1 patient had been using levalbuterol the remainder albuterol as rescue prior to presenting to the ED)	N=547 Varying duration of hospitali-zations	Primary: Hospital admission rate Secondary: LOS, ED LOS, intensification, number of aerosols, requirement for oxygen, and adverse effects	Primary: Compared with the albuterol group (45%), the levalbuterol group (36%) had a significantly lower hospitalization rate (P=0.02). Secondary: There were no significant differences between the albuterol and levalbuterol group concerning secondary outcomes, including adverse effects (P=0.26 to P=0.94). No significant adverse events occurred in either group.
Schreck et al.[32] (2005)	CR, OS, RETRO Individuals 1 year	N=736 9 months	Primary: Patient disposition, ED LOS, and	Primary: There was a significantly lower hospitalization rate in the levalbuterol group compared with albuterol (4.7 and 15.1%; P=0.0016). The rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albuterol 2.5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25 mg via nebulization (plus standard treatment)	of age or older with a diagnosis of acute asthma presenting to the ED requiring nebulization with a SABA		objective measures of patient upon arrival Secondary: Not reported	15.1% is comparable to the hospitals average admission rate of 16.4%. There was no significant difference between the two treatment groups concerning ED LOS and other objective measures upon patient presentation (P=0.762). Due to a decrease in hospitalizations, treatment costs were lower in the levalbuterol treatment group (no P value reported). Secondary: Not reported
Qureshi et al.[33] (2005) Albuterol 2.5-5 mg via nebulization (plus standard treatment) vs levalbuterol 1.25-2.5 mg via nebulization (plus standard treatment)	DB, PRO, RCT Children 2 to 14 years of age with a known history of asthma presenting to a pediatric ED with an acute moderate or severe asthma exacerbation	N=129 Study was complete after patient received 5 doses, was admitted, or discharged	Primary: Changes from baseline in clinical asthma score and the percent of predicted FEV_1 after the 1st, 3rd, and 5th treatment Secondary: Number of treatments, length of ED care, rate of hospitalizations, changes in pulse rate, and oxygen saturation	Primary: No significant differences between the treatment groups were found (no P value reported). Secondary: No significant differences between the treatment groups were found (no P value reported). No significant differences between the treatment groups concerning adverse effects (no P value reported).
Nowak et al.[34] (2006) Albuterol 2.5 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg	DB, MC, PG, PRO, RCT Individuals ≥18 years of age presenting to the ED or clinic with an acute asthma exacerbation	N=627 1 month	Primary: Time to meet ED discharge criteria Secondary: Comparisons of FEV_1 change from baseline, the proportion of	Primary: For the levalbuterol and albuterol groups the median time to discharge (76.0 and 78.5 minutes) was not statistically different (P=0.74). Secondary: There was no significant difference (P=0.28) in the admission rate between the albuterol (9.3%) and the levalbuterol (7.0%) groups. After dose one and cumulative doses over time there was a greater FEV_1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levalbuterol 1.25 mg via nebulization (up to 6 doses in 3 hours) with prednisone 40 mg			patients hospitalized, and the effect of plasma concentration of (S)-albuterol at presentation on FEV_1 response and on hospitalization	improvement following levalbuterol compared with albuterol (P=0.021). For individuals not taking corticosteroids chronically before the trial, there were significantly fewer hospitalizations in the levalbuterol group compared to albuterol (3.8 vs 9.3%; P=0.03). There was no significant difference in the overall frequency of adverse effects in the two treatment groups (no P value reported).
Nelson et al.[35] (1998) Albuterol 1.25 mg via nebulization TID vs albuterol 2.5 mg via nebulization TID vs levalbuterol 0.63 mg via nebulization TID vs levalbuterol 1.25 mg via nebulization TID vs placebo	DB, PC, PG, RCT Patients ≥12 years of age that do not smoke and had at least a 6-month history of chronic and stable asthma, demonstrating at least a 15% improvement in FEV_1 to a single dose of albuterol 2.5 mg via nebulization	N=362 4 weeks	Primary: Peak change in FEV_1 after four weeks Secondary: AUC, use of rescue racemic albuterol meter dose inhaler	Primary: Change in peak FEV_1 in the combined levalbuterol group was not significantly greater than combined albuterol (0.84 and 0.74; no P value reported). Secondary: A similar trend was noticed when evaluating the AUC; after the first dose, levalbuterol treatment was significantly better (P=0.02) compared to albuterol. However, at week four, even though the AUC values were higher in the levalbuterol groups, the difference was not significant. There was a significant improvement (P=0.006) in predose FEV_1 in the combined levalbuterol arm compared to the combined albuterol arm in the subset of patients not taking corticosteroids. There was significantly less rescue medication used in the active treatment groups compared to placebo. Compared to baseline there was a significant decrease in rescue-medication use in both the levalbuterol 1.25 mg arm (P<0.001) and the albuterol 2.5 mg arm (P=0.056). All active treatments were well tolerated with the percent of patients reporting nervousness or tremor in the low dose groups being statistically significantly lower (P=0.003) compared to the high dose groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gawchik et al.[36] (1999) Albuterol 1.25 mg via nebulization (1 dose) vs albuterol 2.5 mg via nebulization (1 dose) vs levalbuterol 0.16 mg via nebulization (1 dose) vs levalbuterol 0.31 mg via nebulization (1 dose) vs levalbuterol 0.63 mg via nebulization (1 dose) vs levalbuterol 1.25	DB, PC, RCT, XO Patients 3 to 11 years of age with a history of asthma for at least 6 months and reversibility of 12% or more 30 minutes after 2.5 mg of albuterol administered by nebulization	N=43 4 treatment visits (2 to 8 days apart)	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC Secondary: Not reported	Primary: Differences in peak change in FEV_1, peak percent change in FEV_1 and AUC was significantly improved in all treatment arms (with the exception of albuterol 1.25 mg in AUC) compared with placebo ($P<0.05$). No significant differences between the treatment groups were found ($P<0.55$). The medications were well tolerated and all adverse events reported were mild or moderate in severity, with no significant difference seen across the treatment groups (no P values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg via nebulization (1 dose) vs placebo (1 dose)				
Milgrom et al.[37] (2001) Albuterol 1.25 mg via nebulization vs albuterol 2.5 mg via nebulization vs levalbuterol 0.31 mg via nebulization vs levalbuterol 0.63 mg via nebulization vs placebo	DB, MC, PC, PG, RCT Patients 4 to 11 years of age with documented diagnosis of at least mild asthma with a reversibility of at least 15% to albuterol	N=338 3 weeks	Primary: Peak percent change in FEV_1 from baseline Secondary: Change in pulmonary function, percent of responders within 30 minutes after dose, time to peak improvement in FEV_1, use of rescue medications, symptoms, symptom-free days, asthma control days, and adverse effects	Primary: A significant improvement was seen in peak percent change in FEV_1 from baseline in all active treatment arms compared with placebo on day 21 ($P<0.019$). Secondary: Immediately after nebulization on days 0 and 21 there were clinically significant changes for all groups except placebo ($P<0.02$) and, with the exception of the albuterol 1.25 mg group, more patients responded to active treatment in comparison to the placebo group on both days ($P<0.02$). On day 0 significantly more patients responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), immediately after nebulization ($P=0.12$). Levalbuterol 0.31 mg achieved a significantly greater change in asthma control days compared to levalbuterol 0.63 mg and albuterol 1.25 mg ($P<0.04$ for each comparison). Compared to all active treatments levalbuterol 0.31 mg produced significantly smaller changes in heart rate ($P<0.02$). A significant decrease in potassium levels was seen in all treatment groups compared to placebo ($P<0.002$).
Nowak et al.[38] (2004)	OL, PRO Adult asthmatics	N=93 2 hours	Primary: FEV_1 percent change from	Primary: The median percent change in FEV_1 was greater for 1.25 mg levalbuterol (74%), compared with 2.5 mg albuterol, (39%), 0.63 mg levalbuterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albuterol 2.5 mg via nebulization (3 doses) vs albuterol 5 mg via nebulization (3 doses) vs levalbuterol 0.63 mg via nebulization (3 doses) vs levalbuterol 1.25 mg via nebulization (3 doses) vs levalbuterol 2.5 mg via nebulization (3 doses) vs levalbuterol 3.75 mg via nebulization (3 doses)	presenting to the ED with an acute asthma exacerbation		baseline following the 3rd nebulization Secondary: Change and percent change from baseline FEV_1 at each time point, the percent of responders, and the time to achieve a 15% and 50% increase from baseline	(37%), and 3.75 mg levalbuterol (26%) after three doses (no P value reported). Secondary: Compared to baseline at 60 minutes post treatment, levalbuterol 1.25, 2.5, and 5.0 mg improved the median percent predicted FEV_1 by 33 to 38% compared to 12 to 24% with 2.5 and 5.0 mg doses of albuterol and 0.63 and 3.75 mg doses of levalbuterol (no P value reported). (S) albuterol levels were found to be significantly inversely correlated with baseline FEV_1 (P=0.004), and percent change in FEV_1 60 minutes post dose (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levalbuterol 5 mg via nebulization (3 doses)				
Skoner et al.[39] (2005) Albuterol 1.25 to 5 mg TID via nebulizer vs levalbuterol 0.31 mg to 0.63 mg TID via nebulizer vs placebo	DB, MC, PC, PG, RCT Children 2 to 5 years of age who have been diagnosed with asthma for at least 30 days and had no other underlying medical condition	N=211 4 weeks	Primary: Change from baseline in the total score on the PAQ Secondary: PEF, rescue medication use, and the Child Health Status Questionnaire	Primary: Decrease in the PAQ scores was demonstrated in all treatment groups (no P value reported). Secondary: All treatment groups demonstrated an improvement in PEF compared to placebo (P<0.01 for all treatment groups). All treatment groups, including the placebo group, demonstrated a decrease in rescue medication use. There were no significant differences between the treatment groups (No P value reported). All treatment groups demonstrated and improvement from baseline in the Child Health Status Questionnaire (no P value reported). Overall, the incidence of adverse events was similar for each treatment group during the study period. Adverse events were mild (68.0%) to moderate (28.1%) in severity. Among all patients, significant increases in ventricular heart rate were demonstrated in the levalbuterol 0.63 mg and racemic albuterol 2.5 mg groups compared to placebo (no P value reported).
Berger et al.[40] (2006) Albuterol HFA 180 µg QID vs levalbuterol HFA 90 µg QID	DB, MC, RCT Patients 4 to 11 years of age with asthma	N=150 28 days	Primary: Peak percent change in FEV_1 Secondary: Area under the FEV_1 percent change from predose curve and peak percent	Primary: Levalbuterol significantly improved the peak percent change in FEV_1 compared to placebo (25.6 vs 16.8%, respectively; P<0.001). There was no significant difference with albuterol compared to placebo (21.8 vs 16.8%, respectively; P=NS). Secondary: Results for levalbuterol were similar for the other spirometry endpoints (P<0.05 vs placebo).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			predicted FEV_1, adverse events	No levalbuterol-treated patients had a peak percent change in FEV_1 <10% compared to 15.8% of albuterol-treated patients and 30.3% of placebo-treated patients. The incidence of adverse events was 43.4% for levalbuterol, 56.4% for albuterol, and 51.4% for placebo. The rate of discontinuation was 1.3% for levalbuterol, 2.6% for albuterol, and 8.6% for placebo. The rate of asthma attacks was similar among treatments (levalbuterol 10.5%, albuterol 12.8%, and placebo 14.3%). The use of rescue medications (days/week) decreased with both active treatments (levalbuterol compared with placebo; P<0.001, albuterol compared with placebo; P<0.01, and levalbuterol compared with albuterol; P>0.05).
Hamilos et al.[41] (2007) Albuterol HFA 180 µg QID vs levalbuterol HFA 90 µg QID	MC, PG, OL Patients ≥12 years of age with mild to moderate asthma (mean FEV_1 68.3W% predicted)	N=745 6 months to 1 year	Primary: Adverse events, Secondary: asthma attacks (requiring hospitalization, a visit to the ED or clinic, or a burst of corticosteroids), rescue medication use, quality of life (Adult Asthma Quality of Life Questionnaire)	Primary: Rates of adverse events were similar with levalbuterol (72%) and albuterol (76.8%; P=0.12). Rates of β-mediated adverse events, serious adverse events, and discontinuations because of adverse events were low (<15%) and were comparable between groups. Rates of asthma adverse events for levalbuterol and racemic albuterol were 18.3 and 19.6%, respectively. Secondary: Rates of asthma attacks were similar between groups. Rates of rescue medication use and daytime asthma control days were similar between groups. Quality of life improved to a similar extent in both groups.
Tripp et al.[42] (2008)	AC, MC, RCT, XO	N=49	Primary: Safety and efficacy	Primary: Heart rate and (R)-albuterol exposure increased for both racemic albuterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albuterol HFA 90 µg per dose (1x, 2x, 4x, 8x, and 16x) administered over a 2-hour period vs levalbuterol HFA 45 µg per dose (1x, 2x, 4x, 8x, and 16x) administered over a 2-hour period	Patients with asthma	Single-day	Secondary: Not reported	HFA and levalbuterol HFA. For cumulative doses of 8x or greater, racemic albuterol HFA treatment had greater increases in mean heart rate than levalbuterol HFA (2.8 beats/min; 95% CI, 0.3 to 5.3). For cumulative doses of 16x, racemic albuterol HFA treatment had greater increases in mean heart rate than levalbuterol HFA (3.5 beats/min; 95% CI, 0.6 to 6.4). (R)-albuterol plasma levels ranged from 10 to 18% higher after racemic albuterol HFA dosing vs after levalbuterol HFA. FEV_1 improvements were similar for both treatments. The relative potencies of the two therapies (based on FEV_1) were similar (ratio, 1.1; 90% CI, 0.9 to 1.2). Secondary: Not reported
Wolfe et al.[43] (1991) Albuterol syrup 2 mg TID vs metaproterenol syrup 10 mg TID	IB, MC, PG, RCT Patients 6 to 9 years of age with chronic asthma	N=65 4 weeks	Primary: Time to maximal response, maximum percent increase from baseline, peak flow measurements, heart rate, blood pressure, adverse effects Secondary: Not reported	Primary: There was a greater degree of bronchodilation with albuterol compared to metaproterenol from two to eight hours post dose ($P<0.05$). The peak percent improvement in $FEV_1$from baseline was significantly greater for albuterol compared to metaproterenol (29.3 vs 20.6%; $P<0.05$). There were no significant differences in the mean change from baseline in systolic blood pressure in either group, however with metaproterenol the chronotropic effect was significantly greater ($P<0.05$) at one hour on day one and 28 and 1.5 hour on day 28 compared to albuterol. There was no significant difference in the frequency of adverse effects between the two groups. Secondary: Not reported
Habib et al.[44] (1987) Albuterol 5 mg via	DB, RCT Patients reversible airway obstruction	N=20 7 days	Primary: Lung function and adverse events	Primary: There were no significant differences observed between the spirometric responses or the adverse effects of the two groups to either agent.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nebulizer vs metaproterenol 15 mg via nebulizer	utilizing intermittent positive pressure ventilation		Secondary: Not reported	Secondary: Not reported
Papi et al.[45] (2007) Albuterol 100 µg as needed (as needed albuterol) vs beclomethasone-albuterol 250/100 µg in a single inhaler as needed (as needed combination) vs beclomethasone 250 µg BID and albuterol 100 µg as needed (regular beclomethasone) vs beclomethasone-albuterol 250/100 µg BID in a single inhaler and albuterol 100 µg as	DB, DD, MC, PG, RCT Patients 18 to 65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after inhalation of 200 µg of albuterol or a positive methacholine challenge	N=455 6 months	Primary: Mean rate of morning PEFR Secondary: Lung function, symptom scores, and number/severity of exacerbations	Primary: The morning PEF rate at six months was significantly higher among patients receiving as-needed combination therapy and in for patients receiving regular beclomethasone therapy compared to the use of as-needed albuterol therapy. The morning PEF rate did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary: The evening PEF rate was significantly higher in the group receiving regular beclomethasone therapy, but not in the group receiving as-needed combination therapy compared to as-needed albuterol therapy. The pre bronchodilator FEV_1 and FVC were significantly higher after as-needed combination therapy, but not after regular beclomethasone therapy compared with as-needed albuterol therapy. These values did not differ significantly between patients receiving as-needed combination therapy and those receiving regular beclomethasone therapy or regular combination therapy. The FEV_1 and FVC increased significantly in the as-needed combination group and in the regular combination group, and evening PEF rate increased significantly in the regular combination group. The evening PEF rate and FEV_1 (percentage of the predicted value) increased significantly in the regular beclomethasone group. The group receiving as-needed combination therapy had fewer nocturnal awakenings, and the group receiving regular beclomethasone had less daily use of rescue medication compared to as-needed albuterol therapy. The percentage of symptom-free days was significantly higher in the group receiving regular beclomethasone therapy than in the group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed (regular combination)				receiving as-needed albuterol therapy. The percentage of symptom-free days increased significantly in all groups, except the group receiving as-needed albuterol therapy, in which the number of nocturnal awakenings increased significantly. The regular beclomethasone group had fewer daytime asthma symptoms at 6 months than at baseline. A total of 237 exacerbations occurred during the study, 38 in patients receiving as-needed combination therapy, 83 in those receiving as-needed albuterol therapy, 33 in those receiving regular beclomethasone therapy, and 83 in those receiving regular combination therapy. The mean number of exacerbations per patient per year was lower in the as-needed combination group (0.74) and in the regular beclomethasone group (0.71) than in the as-needed albuterol group (1.63; P<0.001) and in the regular combination group (1.76; P<0.001). The percentage of patients with at least one exacerbation was not significantly different in the group receiving as-needed combination therapy (4.92%) and the group receiving regular beclomethasone therapy (5.66%; P=0.802) or the group receiving regular combination therapy (10.09%; P=0.133). The percentage of patients with at least one exacerbation was significantly lower both in the group receiving as-needed combination therapy and in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (17.80%) (P=0.002 and P=0.005, respectively). The time to first exacerbation differed significantly between groups, with the shortest time to first exacerbation in the as-needed albuterol group (P=0.003 by the log-rank test).
Rabe et al.[46] (2006) Budesonide-formoterol 160/4.5 µg BID and terbutaline	DB, MC, PG, RCT Patients >12 years of age with asthma who had >1 severe asthma exacerbation in the 12 months	N=3,394 12 months	Primary: Time to first severe exacerbation Secondary: Total number of severe	Primary: The time to first severe exacerbation was longer with as needed budesonide-formoterol vs formoterol (P=0.0048) or terbutaline (P<0.0001). As-needed formoterol prolonged the time to first severe exacerbation vs terbutaline (P=0.0051). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MDI 0.4 mg as needed vs budesonide-formoterol 160/4.5 µg BID and formoterol MDI 4.5 µg as needed vs budesonide-formoterol 160/4.5 µg BID and budesonide-formoterol 160/4.5 µg as needed	before entry, use of inhaled corticosteroids for >3 months and at a constant dose for ≥4 weeks immediately before entry, FEV_1 50 to 100% of predicted normal (pre bronchodilator) with 12% reversibility or more after inhalation of terbutaline 1 mg		exacerbations, time to first and total number of emergency treatment or hospitalizations, asthma symptom scores—asthma control questionnaire score; mild exacerbations; FEV_1; morning and evening PEF; and reliever medication use	As-needed budesonide-formoterol reduced the risk of a severe exacerbation by 27% (95% CI, 10 to 41) vs formoterol and by 45% (95% CI, 32 to 55) vs terbutaline. The risk reduction with as-needed formoterol vs terbutaline was 24% (95% CI, 8 to 37). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% vs formoterol (P<0.0001), by 48% vs terbutaline (P<0.0001), and by 22% with as-needed formoterol vs terbutaline (P=0.012; table 2). Rates of exacerbations needing emergency room treatment or hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) vs formoterol and by 39% (P=0.0010) vs terbutaline, respectively. There was no significant difference between formoterol and terbutaline. The proportion of patients with more than one exacerbation was lowest in the as-needed budesonide-formoterol group (3, 7, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively). Mild exacerbation days were reduced by 10 to 18% with as-needed budesonide-formoterol compared with both formoterol P=0.043) and terbutaline (P<0.0001). The time to first mild exacerbation was longer with as-needed budesonide-formoterol vs terbutaline (P=0.0080), but the difference between as-needed budesonide-formoterol and formoterol was not significant (P=0.059). Mean asthma symptom scores decreased for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group vs maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (seven nights per year) with as-needed budesonide-formoterol vs formoterol (P=0.018) and by 3% vs terbutaline (P=0.0025). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				or night-time awakenings. Asthma-control days increased in all groups with no between-group differences. Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (P=0.0009) and terbutaline (P<0.0001). No difference in overall ACQ-5 scores was seen with formoterol vs terbutaline. Mean FEV_1 improved in each of the treatment groups when all patients used maintenance budesonide-formoterol plus as-needed terbutaline (run-in). Additional increases in FEV_1 of 0.05 L and 0.08 L were seen with as-needed budesonide-formoterol vs formoterol (P=0.0001) and terbutaline (P<0.0001). Mean morning PEF increased from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol vs both formoterol (4.8 L per min; P=0.004) and terbutaline (7.5 L per min; P<0.0001). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5.4 L per min; P=0.0011) and terbutaline (6.3 L per min; P=0.0001). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline. The mean reliever use decreased to 1.02 inhalations per day in the budesonide-formoterol group and to 1.23 and 1.26 inhalations per day in the formoterol and terbutaline groups, respectively. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (P<0.0001 for both) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups.
Pohunek et al.[47] (2006)	AC, DB, MC, PG, RCT	N=630 12 weeks	Primary: Change in morning PEFR	Primary: The change in morning PEFR was significantly greater with budesonide-formoterol compared with budesonide (mean difference 10.9 L/min;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol 80/4.5µg BID (fixed-dose inhaler) vs budesonide 100 µg 2 puffs BID vs budesonide 100 µg 2 puffs BID and formoterol 4.5 µg 2 puffs BID (separate inhalers)	Patients 4 to 11 years of age with PEF >50% of predicted normal who had received stable treatment with an inhaled corticosteroid, and history of an average of ≥1 clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study		Secondary: Change from baseline in: evening PEF; total asthma-symptom score; night-time awakenings due to asthma symptoms; use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change in health-related quality of life (PAQLQ)	P<0.001). There was no significant difference in morning PEF between patients treated with budesonide-formoterol and those who received budesonide + formoterol in separate inhalers (P=0.14). Secondary: Significantly greater changes in evening PEF were seen in patients treated with budesonide-formoterol compared to budesonide (mean difference 9.1 L/min; P<0.001). There was no significant difference between budesonide-formoterol and budesonide + formoterol in separate inhalers. Patients treated with budesonide-formoterol had significantly greater changes in FEV_1 compared with budesonide (mean difference 0.078 L; P<0.001). There was no significant difference between budesonide-formoterol and budesonide + formoterol in separate inhalers. Asthma symptoms improved from baseline with all treatments, with no significant between-group differences. Overall PAQLQ(S) scores improved in all treatment groups, with adjusted mean changes of 0.437, 0.494 and 0.501 for the budesonide-formoterol, budesonide + formoterol in separate inhalers and budesonide treatment groups, respectively. No significant between-group differences were observed. Scores were also improved for the individual domains, indicating improvements with regard to symptoms, emotional function and activity limitation; there were no differences between the treatment groups.
Peters et al.[48] (2016) Budesonide and formoterol 80/4.5 µg or 160/4.5 µg two puffs inhaled BID vs	DB, MC, RCT Patients ≥ 12 years of age with a diagnosis of persistent asthma, daily asthma medication use, and with one to four asthma exacerbations in the	N= 11,693 26 weeks	Primary: First serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization) Secondary: First asthma	Primary: A serious asthma-related event occurred in 43 patients who were receiving budesonide-formoterol and in 40 patients who were receiving budesonide alone (HR, 1.07; 95% CI, 0.70 to 1.65). Budesonide-formoterol was shown to be noninferior to budesonide alone. There were two asthma-related deaths, both in the budesonide-formoterol group. One of these patients had undergone an asthma-related intubation. Secondary: In the budesonide/formoterol group, 539 patients (9.2%) reported a total of

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budesonide 80 µg or 160 µg two puffs inhaled BID (patients were stratified to a dose of budesonide based on pre-study asthma control as assessed by ACQ-6 and prior asthma therapy)	previous year.		exacerbation, asthma control, and symptom control	637 exacerbations. In the budesonide group, 633 patients (10.8%) reported a total of 762 exacerbations. The risk of an asthma exacerbation was 16.5% lower with budesonide-formoterol than with budesonide alone (HR, 0.84; 95% CI, 0.74 to 0.94; P=0.002). There was a statically significant improvement in asthma control in both treatment groups. A greater improvement was observed with budesonide-formoterol (average decrease from baseline ACQ-6, −0.67) than with budesonide alone (average decrease from baseline ACQ-6, −0.58) P<0.001. Budesonide-formoterol was superior to budesonide alone in all of the variables assessed related to symptom control (including a greater mean number of symptom-free days, fewer night-time awakenings, and the use of fewer doses of rescue medication), except for limitation of activity because of asthma.
Hardy et al.[49] (2019) PRACTICAL Reliever therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler (one inhalation as needed for relief of symptoms) vs maintenance budesonide 200 µg Turbuhaler (one inhalation twice daily) plus terbutaline 250 µg Turbuhaler (two	MC, OL, PG, RCT Adults 18 to 75 years of age with a self-reported doctor's diagnosis of asthma who were using SABA for symptom relief with or without maintenance low to moderate doses of inhaled corticosteroids in the previous 12 weeks	N=885 52 weeks	Primary: Number of severe exacerbations per patient per year Secondary: Time to first severe exacerbation, combined moderate and severe asthma exacerbation rate, safety	Primary: The rate of severe asthma exacerbations was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline therapy (absolute rate per patient per year, 0.119 vs 0.172; relative rate, 0.69; 95% CI, 0.48 to 1.00; P=0.049). Secondary: Time to first severe exacerbation was longer with budesonide–formoterol than budesonide maintenance plus as-needed terbutaline. The number of severe exacerbations resulting in an emergency department visit or hospital admission was five and zero, respectively, with as-needed budesonide-formoterol and seven and two, respectively, with budesonide maintenance plus as-needed terbutaline. The combined moderate and severe asthma exacerbation rate was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline (absolute rate per patient per year, 0.165 vs 0.237; relative rate, 0.70; 95% CI, 0.51 to 0.95; P=0.024). Time to first moderate or severe exacerbation was longer with as-needed budesonide–formoterol than budesonide maintenance. The number of patients who were withdrawn because of treatment failure did not differ between groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalations as needed)				(nine in the budesonide–formoterol group vs 11 in the budesonide maintenance plus terbutaline group; relative risk, 0.84; 95% CI, 0.35 to 2.00; P=0.69). Nasopharyngitis was the most common adverse event in both groups, occurring in 35% of patients receiving as-needed budesonide–formoterol and 32% of receiving maintenance budesonide plus terbutaline. The number of participants with at least one adverse event was 385 (88%) in the budesonide–formoterol group and 371 (83%) in the budesonide–maintenance plus terbutaline group. There were two hospital admissions due to asthma in the budesonide maintenance group. There were no deaths in the study.
Peters et al.[50] (2007) LOCSS Fluticasone 100µg BID vs montelukast 5 to 10 mg QD vs fluticasone-salmeterol 100-50µg QHS	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator, reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/ml within the previous 2 years. Patients were stable on fluticasone 100 µg BID and step-down therapy was being attempted.	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of pulmonary function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	Primary: The rates of treatment failure were 20.2% in the fluticasone group, 20.4% in the fluticasone/salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary: Mean pre bronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone-salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the Asthma Control Questionnaire, was better in the fluticasone group and in the fluticasone-salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone-salmeterol group (22.9 vs 17.1%; P=0.06) and in the fluticasone group (22.9 vs 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone group than in the montelukast group (16.7 vs 25.4%; P=0.04), with a similar trend in the fluticasone-salmeterol group (17.3 vs 25.4% in the montelukast group; P=0.06).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6 to 85.8%.
Boonsawat et al.[51] (2003) Formoterol 18 µg administered at 0, 30, and 60 minutes vs albuterol 100 µg administered at 0, 30, and 60 minutes	DB, DD, PG, RCT Patients 18 to 67 years of age with asthma presenting to the ED with acute bronchoconstriction	N=88 1 day	Primary: FEV_1, asthma symptoms Secondary: Not reported	Primary: A non-significant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; P=0.18). There was a significant increase in the maximum FEV_1 between 75 to 240 and 15 to 45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51 vs 36%; P<0.05). Subjective symptom score assessments decreased during the course of the study. Secondary: Not reported
Lee-Wong et al.[52] (2008) Formoterol 12 µg every 30 minutes, up to 2 treatments vs albuterol 2.5 µg via nebulization every 30 minutes, up to 2 treatments	RCT Patients 18 to 65 years of age who presented to the ED with mild to moderate asthma exacerbation (PEFR 40 to 60% of predicted)	N=34 1 treatment period	Primary: Symptom scores and PEFR Secondary: Not reported	Primary: At 30 and 60 minutes, the mean PEFR of the albuterol group increased from 43.7% of predicted to 51.9% of predicted and 54.6% of predicted, respectively. The formoterol group had changes in the mean PEFR from 49.3% of predicted to 55.5% of predicted and 57.3% of predicted, respectively. The mean change in the two groups was not significantly different at 30 and 60 minutes (P=0.64 and P=0.57, respectively). Symptom scores improved in the albuterol group by 3.7 and 5.5 from 0 minutes to 30 and 60 minutes, respectively. In the formoterol group, these values were 3.1 and 4.9 at 30 and 60 minutes, respectively. The mean change in the two groups was not significantly different at 30 and 60 minutes (P=0.61 and 0.76, respectively). Secondary: Not reported
Pauwels et al.[53] (2003) Formoterol 4.5 µg	MC, OL, RCT Patients ≥6 years of age with asthma	N=18,124 6 months	Primary: Asthma-related and non-asthma-related SAE,	Primary: The number of adverse effects was not statistically significant between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as needed vs albuterol 200 µg administered as needed	requiring the use of beta-adrenergic agonists as reliever medication		discontinuation due to adverse effects, and time to first exacerbation Secondary: Rescue reliever mediation	There was a significantly higher number of asthma-related due to adverse event with formoterol compared to albuterol (1 vs 0.5%; P<0.001). Compared with albuterol, there was a significantly longer time to first asthma exacerbation than with formoterol (P<0.001). Secondary: Rescue inhaler use decreased in both groups over the course of the study, with a significantly greater decrease seen in the formoterol group (P<0.001).
Molimard et al.[54] (2001) Formoterol 12 µg and albuterol aerosol inhaler to use as needed vs albuterol 100 µg per inhalation to be used throughout the day on demand (ODS)	MC, OL, PG, RCT Patients ≥18 years of age with moderate persistent asthma	N=259 3 months	Primary: The mean change in morning predose PEF Secondary: Mean increase in evening predose PEF for the entire treatment period, and day and night use of albuterol and scores on the SGRQ	Primary: There was a higher mean increase in the morning PEF in the formoterol group than in the ODS group (25.7 and 4.5 L/min (P<0.0001). Secondary: At visits three and five there was a significantly greater improvement in predose FEV_1 with formoterol compared to ODS (P<0.01, P<0.05). At the conclusion of three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were: -0.8 and -0.4 with formoterol and 0.1 and 0.1 for ODS (P<0.0001). There was a significantly higher increase in symptom-free days and nights in the formoterol group when compared to ODS (20%, 30%; P<0.0001, P<0.003). A significantly higher decrease was seen in the SGRQ score with formoterol (-6.4) compared to ODS (-3.5) (P=0.05).
Pleskow et al.[55] (2003) Formoterol 12 µg BID vs formoterol 24 µg	DB, DD, MC, PC, PG, RCT Patients 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: At the 12-hour mark, both formoterol groups showed significant improvements in FEV_1compared to placebo and albuterol (P<0.001 and P<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: Both formoterol groups showed significant improvements at all time points vs placebo (P<0.001) with the exception of formoterol 12 µg at time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs albuterol 180 µg QID vs placebo				0. Both groups also showed significant improvement compared to albuterol at time 0, 2 to 6 hours, and 10 to 12 hours (P<0.001 and P<0.002). In the albuterol group, there was a significant difference at all time points compared to placebo, except 0, 4 to 6 and 10 to 12 hours (P<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (P<0.001), formoterol 24 µg compared to albuterol (P<0.001) and albuterol compared to placebo (P<0.008) at all visits. Both medications were well tolerated with no significant difference between them.
Wolfe et al.[56] (2006) Formoterol 24 µg BID vs formoterol 12 µg BID, with up to 2 additional 12 µg daily doses of formoterol as needed for worsening symptoms (12 µg bid plus on demand) vs formoterol 12 µg BID	DB, MC, PC, RCT Patients ≥12 years of age with persistent asthma, FEV_1 ≥40% of predicted normal, and FEV_1 reversibility ≥12% after treatment with albuterol	N=2,085 16 weeks	Primary: SAE Secondary: Not reported	Primary: Nine patients had SAEs requiring hospitalization: two patients (0.4%) in the 24 µg BID group; one patient (0.2%) in the 12 µg BID plus on demand group; five patients (0.9%) in the 12 µg BID group; one patient (0.2%) in the placebo group. All events were asthma-related, except for two SAE in the 12 µg BID group that were later considered not to be asthma-related by independent reviewers who were not associated with the conduct of the study. Proportions of patients with SAE (requiring systemic corticosteroids) were similar in the 24 µg BID group (6.3%), 12 µg BID group (5.9%) and placebo group (8.8%) and lower in the 12 µg BID plus on demand group (4.4%; P=0.0057 vs placebo). All formoterol treatment regimens had a significant effect on FEV_1 measured 2 hours after dose during the study (P<0.0001 vs placebo); and on predose trough FEV_1 measured at all visits after baseline (P<0.002 vs placebo). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Bouros et al.[57] (1999) Formoterol 12 µg BID and beclomethasone 500 µg daily vs beclomethasone 1,000 µg daily	MC, OL, PG, RCT, PG Patients ≥18 years of age with asthma who were symptomatic on 500 µg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final seven days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication, and safety	Primary: There was a treatment effect of 20.36 L/min in the combination group over the patients receiving the double dose of steroid (P=0.021). Secondary: For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of steroid (P<0.05). There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination treatment arm (night P=0.001, day P<0.001). In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the steroid (night P=0.003, day P<0.001) There was no significant difference in adverse events in either group.
Stelmach et al.[58] (2016) Ciclesonide 160 µg inhaled QAM and formoterol 4.5 µg inhaled QAM and QPM vs ciclesonide 160 µg inhaled QAM and montelukast 5 mg or 10 mg PO QPM	DB, PC, PRO, RC Children ages 12 to 18 years of age with a diagnosis of asthma and postexercise symptoms in the past 6 months despite chronic ICS treatment	N=80 8 weeks	Primary: Clinical symptoms as measured by a daily diary card. Secondary: Maximum percentage decrease in FEV_1 after exercise and FeNO in exhaled breath after exercise.	Primary: A significant decrease in daytime symptoms from baseline was seen in all groups except the ciclesonide + montelukast group. Mean daily symptoms were scored from 0 points (minimum) to 3 points (maximum). The median daytime symptom scores at baseline verses post study were 0.29 vs 0.19 in the ciclesonide 160 µg group (P=0.0303), 0.57 vs 0.26 in the ciclesonide 320 µg group (P=0.0084), 0.64 vs 0.29 in the ciclesonide + montelukast group (P=0.1213), and 0.43 vs 0.21 in the ciclesonide + formoterol group (P=0.0463). No statistically significant improvement in nighttime symptoms was observed in any of the treatment groups. Secondary: The change from baseline in the maximum decrease in FEV_1 reached the level of significance in all groups except the ciclesonide 160 µg group. The change from baseline in post-exercise FeNO only achieved

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ciclesonide 160 µg inhaled QAM vs ciclesonide 320 µg inhaled QAM				significance in the ciclesonide 320 µg group.
Ralston et al.[59] (2005) Levalbuterol 1.25 mg via nebulization (≤6 doses) vs albuterol 5 mg and ipratropium 0.25 mg via nebulization (≤3 doses) followed by albuterol 5 mg via nebulization (≤3 doses)	DB, PRO, RCT Patients 6 to 18 years of age with a history of asthma (any severity), ability to use a peak flow meter, and PEF <80% predicted upon presentation to the ED	N=154 1 day	Primary: ED LOS Secondary: Percent change in PEF, percent change in heart rate, number of nebulized treatments until disposition, frequency of adjunctive treatment in ED, frequency of unplanned return to medical facility within 72 hours of discharge	Primary: The ED LOS was not significantly different among the treatment groups (P=0.130). Secondary: Significantly more patients in the albuterol/ipratropium group were given systemic steroids (P=0.014). No other secondary endpoints were statistically significant between groups (P=0.257 to P=1.00).
Tinkelman et al.[60] (1990) Metaproterenol via inhalation vs	DB, MC, PG Asthmatic patients	N=133 12 weeks	Primary: Onset of action, peak effect, side effects, and tolerance Secondary: Not reported	Primary: There was no clinical difference between the two treatment groups in the outcomes. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pirbuterol via inhalation				
Boulet et al.[61] (1997) Salmeterol 50 µg BID vs albuterol 200 µg QID	DB, MC, PG, RCT Patients ≥12 years of age with mild to moderate asthma requiring daily pharmacotherapy for at least 6 months	N=228 15 weeks	Primary: FEV_1 Secondary: PEF, symptoms, use of rescue medication, adverse events	Primary: Salmeterol treatment resulted in a significantly greater mean improvement in FEV_1 compared with albuterol treatment from hours 3 to 6 (P<0.001) and 10 to 12 (P<0.012). This effect was maintained throughout the study. Secondary: A significant improvement in evening PEF was seen for salmeterol-treated patients compared to albuterol (34 vs 6 L/min; P<0.001). The average percent increase of symptom free days in the salmeterol group was significantly greater than albuterol (29 vs 15%; P=0.012). There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated.
Faurschou et al.[62] (1996) Salmeterol 100 µg BID and on-demand albuterol vs albuterol 400 µg and on demand albuterol	DB, DD, MC, PG, RCT Patients ≥18 years of age with asthma currently receiving ICS	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1, and patient and physician assessment of efficacy	Primary: The mean morning PEFR improved by 33 L/min in the salmeterol group compared to 4 L/min in the albuterol group at the conclusion of the study (P<0.001). There was a significant reduction in diurnal variation in the salmeterol group (39 to 22 L/min) compared to the albuterol group (34 to 37 L/min; P<0.001). Secondary: Salmeterol increased FEV_1 after three and six weeks compared to baseline significantly more than albuterol (P<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group (P<0.001); however, there was no significant difference in symptom-free days. There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol-treated group (P<0.04).
Martin et al.[63]	DB, DD, MC, RCT,	N=56	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) Salmeterol 84 µg BID vs albuterol extended-release tablets 4 mg in the morning and 8 mg in the evening	XO Patients 18 to 65 years of age with FEV_1 >50% and 12% improvement following inhaled albuterol	8 weeks	Morning peak flow, FEV_1 measurements Secondary: Nocturnal symptoms, nights without awakenings, rescue inhaler use, safety analysis	PEF and FEV_1 were significantly improved in both treatment groups (P<0.001), but there was no significant differences among the treatment groups. Secondary: There was a significant improvement in the percentage of nights without awakenings with salmeterol compared to albuterol (84.6 vs 79.4; P=0.021) There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings. A significant decrease in baseline puffs per day of a rescue inhaler was observed in both the salmeterol (4.57 to 1.85; P<0.001) and the extended release albuterol tablets (4.57 to 2.66; P<0.001). The decrease with salmeterol was significantly greater (P<0.001). A total of 78% of the patients treated with extended release albuterol tablets and 75.9% of patients treated with salmeterol listed adverse effects during the study. A difference that was not statistically significant.
Campbell et al.[64] (1999) Salmeterol Accuhaler (SM DPI) or pressurized MDI (SM MDI) 50 µg BID for 8 weeks, then cross-over to eformoterol* for 4 weeks vs eformoterol* Turbuhaler (eFM)	OL, RCT, XO Patients ≥12 years of age with mild to moderate persistent asthma who were not adequately controlled on ICS	N=469 12 weeks	Primary: Asthma symptoms, nocturnal awakenings, exacerbations, hospital admissions Secondary: Not reported	Primary: There was no significant difference in asthma symptoms between the treatment groups (percent of days symptom-free and using no rescue medicine to relieve symptoms: eFM, 32.8 vs SM DPI, 24.1 vs SM MDI, 28; P=NS). There was no significant difference in nocturnal awakenings between the treatment groups. Patients in all treatment groups gained an additional 1 to 1.5 nights undisturbed by asthma per week; P=NS). There was no significant difference in exacerbations between the treatment groups. The mean number of episodes of worsening of asthma per patient were 0.12 (eFM), 0.13 (SM DPI), and 0.12 (SM MDI; P=0.9144 for eFM vs SM DPI, P=0.9041 for eFM vs SM MDI). There was no significant difference in the percent of patients with worsening asthma between the treatment groups: 11 (eFM), 12 (SM DPI), and 12 (SM MDI; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 µg BID for 8 weeks, then cross-over to salmeterol for 4 weeks				There was no significant difference in the number of episodes of worsening asthma resulting in short course of oral or nebulized steroids: 13 (eFM), 5 (SM DPI), and 11 (SM MDI; P values not reported). There was no significant difference between the treatment groups in hospital admissions or visits to the ED (P values not reported). There was no significant difference between the treatment groups in the number of admissions/visits: 1 (eFM), 1 (SM DPI), and 2 (SM MDI). The Turbuhaler was preferred by patients given both Turbuhaler and a pressurized MDI (P=0.0168) and was considered to be more convenient to carry around than the Accuhaler (P<0.0001). No other differences were found between the three devices. Secondary: Not reported
Everden et al.[65] (2004) Salmeterol DPI (SM DPI) 50 µg BID vs eformoterol* Turbuhaler (eFM) 12 µg BID	OL, PG, RCT Patients 6 to 17 years of age with moderate persistent asthma who were not adequately controlled on ICS	N=156 12 weeks	Primary: Changes in daytime reliever β_2-agonist therapy, total 24-h reliever use, symptom scores, patient and care giver health-related quality of life Secondary: Not reported	Primary: Daytime reliever use decreased significantly from baseline by 65% in the eformoterol group and by 52% in the salmeterol groups (P<0.001). Compared with salmeterol, eformoterol produced a greater decrease in daytime (-0.46 inhalations/day; P=0.081) and 24 hour (-0.70 inhalations/day; P=0.043) reliever use. The percentage of patients who did not require any reliever medication during the study was significantly higher in the eformoterol group (P<0.05 vs salmeterol at weeks eight and 12). There was no significant difference in asthma symptoms between the treatment groups. The overall daytime symptom scores were -0.70 (eFM) compared to -0.53 (SM DPI; 95% CI, -0.36 to 0.02; P=0.052). There was no significant difference in the overall night-time symptom scores between the treatment groups: -0.50 (eFM) compared to -0.47 (SM DPI; 95% CI, -0.22 to 0.17; P=0.687).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in poorly controlled days per patient per 12 weeks: 12.4 (eFM) vs 17.0 (SM DPI; P=0.107). There was no significant difference in the median days time to achieve pre-defined criteria for asthma control: 12 (eFM) vs 26 (SM DPI; P=0.175). There was no significant difference in nocturnal awakenings (nights per week): -1.03 (eFM) vs -1.31 (SM DPI; 95% CI, -0.36 to 0.92); P=0.632). There was no significant difference in the percent of patients experiencing a severe exacerbation: 17 (eFM) vs 17 (SM DPI; P=NS). There was no significant difference in the frequency of mild exacerbations per patient per 12 weeks: 7.8 (eFM) vs 12.2 (SM DPI; P=0.051). There was no significant difference in quality of life between the treatment groups (P=NS). There was no significant difference in the amount of missed work among the treatment groups. The proportion of days in which parents were unable to attend work or participate in leisure activities because of child's asthma was 0.76% with eFM compared to 3.52% with SM DPI (P=0.071). There was no significant difference in the amount of missed school (1 to 2% of days in both groups; P=NS). There was no significant difference in compliance rates among the treatment groups (90 vs 88%; P=NS). Secondary: Not reported
Vervloet et al.[66] (1998) Salmeterol 50 µg	MC, OL, PG, RCT Patients ≥18 years of age with	N=482 6 months	Primary: Asthma symptoms, rescue medication use, quality of life,	Primary: There was no significant difference in asthma symptoms. The number of episode-free days per patient per six months was 97 (formoterol) compared with 95 (salmeterol; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs formoterol 12 µg BID	moderate to severe asthma and currently using regular ICS		missed days of work, emergency room visits, and inpatient hospitalization days Secondary: Not reported	There was no significant difference in rescue medication use. The mean number of puffs per patient per six months was 199 (formoterol) compared with 203 (salmeterol); P=0.406). There was no significant difference in quality of life. The percentage of patients reaching a clinically relevant improvement in quality of life after 6 months of treatment was 64 (formoterol) compared with 62 (salmeterol; P=NS). There was no significant difference in the number of missed days of work. The mean number of days of absence from paid work per patient per six months was 3.19 (formoterol) compared with 2.64 (salmeterol; P=0.144). There was no significant difference in emergency room visits (mean per patient per six months): 0.027 (formoterol) compared with 0.095 (salmeterol; P=0.188). There was no significant difference in the number of inpatient hospitalization days (mean number of days per patient per six months): 0.58 (formoterol) compared with 0.43 (salmeterol); P=0.996). Secondary: Not reported
Condemi et al.[67] (2001) Salmeterol 50 µg BID vs formoterol 12 µg BID	MC, OL, PG Patients 18 to 75 years of age with moderate to moderately severe asthma and currently on ICS	N=528 6 months	Primary: Mean morning PEF measured five minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue	Primary: There was a significant increase in mean PEF values measured five minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 vs 371.7 L/min; P<0.001). Secondary: Individuals receiving formoterol reported using significantly fewer actuations of rescue medication per week within 30 minutes of dosing (1.4 vs 2.1; P<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; P<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; P<0.03) compared to salmeterol.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			medications, symptom score, overall mean morning predose PEF, and safety	Patients experienced significantly more episode free days in the formoterol group compared to salmeterol (9.5 vs 7.8; P<0.04). Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments.
Schermer et al.[68] (2004) Salmeterol 50 µg BID vs formoterol 12 µg BID vs placebo	DB, MC, PC, RCT, XO Patients with moderate persistent asthma	N=35 2 weeks	Primary: FEV_1 and VAS scores, PEFR, and use of rescue medications Secondary: Not reported	Primary: Formoterol and salmeterol both caused a significant increase in FEV_1 (0.45 L [95% CI, 0.01 to 0.80] and 0.27 L [95% CI, 0.08 to 0.62] respectively). At three minutes post-dose, more patients demonstrated an onset of action (≥15% increase in FEV_1) with formoterol than salmeterol (36 vs 13%; P=0.063), as well as at six hours post-dose (42 vs 27%; P=0.063). VAS scores were similar for formoterol and salmeterol at the pre-treatment assessment, but tended to be higher with formoterol after two weeks treatment. There was no difference between formoterol and salmeterol with regards to PEFR values or the use of rescue medication. Fifty percent of patients preferred formoterol compared to 29% of patients receiving salmeterol (P<0.001). Significant associations between FEV_1 and VAS ratings existed only at 10, 15 and 30 min post-dose time points not before or after these time points. Secondary: Not reported
Nightingale et al.[69] (2002) Salmeterol 50 µg BID vs	PC, RCT, XO Patients with severe asthma whose symptoms were not being controlled by high doses of ICS (≥1,500 µg/day) or	N=42 4 weeks	Primary: Morning pre-treatment PEF, FEV_1, FVC, evening PEF, symptom scores, and use of rescue medications	Primary: The mean morning PEF was greater in patients receiving formoterol (mean increase, 14.4 L/min) or salmeterol (mean increase, 14.8 L/min) compared with those receiving placebo, but there was no difference between these treatments. There were no significant treatment effects for any other outcome measures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 12 µg BID vs placebo	with regular oral corticosteroid		Secondary: Not reported	Secondary: Not reported
Brambilla et al.[70] (2003) Salmeterol 50 µg BID and on-demand albuterol vs formoterol 12 µg BID and on-demand albuterol vs on-demand albuterol	MC, OL, PG, RCT Patients ≥18 years of age with moderate to severe persistent asthma suboptimally controlled on ICS and on-demand albuterol (with or without salmeterol)	N=6,239 4 weeks	Primary: Difference in evening predose PEF between patients continued on salmeterol and those switched to formoterol Secondary: Morning predose PEF, asthma symptom score, use of rescue inhaler	Primary: A significant increase in mean evening predose PEF was seen in patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/min; P<0.001) and albuterol as needed (409.3 vs 385 L/min; P<0.001). Secondary: In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom free days, a significant reduction in rescue medication use (all P<0.001). There was no significant difference in the incidence of adverse effects between treatment groups.
Brambilla et al.[71] (1994) Salmeterol 50 µg BID vs terbutaline 5 mg SR tablets BID	DB, DD, MC, PG, RC Patients 18 to 67 years of age with asthma and >15% reversibility after inhaled albuterol	N=159 2 weeks	Primary: Number of awakening-free nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	Primary: In the salmeterol group, the mean number of awakening-free nights over the last week of treatment was significantly higher than with the terbutaline SR (5.3 vs 4.6; P=0.006). Secondary: No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline SR on morning PEF (P=0.04) and PEF daily variations (P=0.01). A significantly greater percent of individuals in the salmeterol group (30%) compared to the terbutaline group (9%) stopped using rescue albuterol during the day (P=0.004), but there was no significant difference at night.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly fewer patients in the albuterol group reported adverse events (16 vs 29%; P=0.04).
Estelle et al.[72] (1997) Salmeterol 50 µg BID vs beclomethasone 200 µg BID vs placebo	DB, PC, PG, RCT Patients 6 to 14 years of age with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse effects	Primary: During months one to two of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (P=0.003) or placebo (P<0.001); however, this difference was lost two weeks after discontinuation of treatment. Secondary: In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (P=0.002 and P=0.02, respectively) with the similar effects seen with beclomethasone and salmeterol. Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (P<0.001, P=0.03); however, the difference between salmeterol and placebo was not significant. Height in the beclomethasone-treated children increased by 3.96 cm during months one to 12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; P=0.018) and the salmeterol-treated children (5.40 cm; P=0.004).
Lemanske et al.[73] (2010) BADGER Salmeterol 50 µg BID+fluticasone 100 µg BID (LABA step-up therapy) vs fluticasone 250µg	DB, RCT, XO Patients 6 to 17 years of age with uncontrolled asthma (diary-reported symptoms, rescue use of an inhaled bronchodilator with ≥2 puffs/day, or peak flows <80% of the predetermined reference value)	N=165 48 weeks	Primary: Differential response to each of the three step-up therapies on the basis of fixed threshold criteria for the following three asthma-control measures: need for treatment with oral prednisone for	Primary: A differential response occurred in 161 of 165 patients (98%; P<0.001). The proportion of patients who had a better response to LABA step-up was higher than the proportion with a better response to LTRA step-up (52 vs 34%; P=0.02), and the proportion with a better response to LABA step-up was higher than the proportion with a better response to ICS step-up (54 vs 32%; P=0.004), whereas the responses to LTRA and ICS step-up therapies were similar. The response to LABA step-up therapy was significantly more likely to be the best response, as compared with the response to LTRA step-up (relative probability, 1.6; 95% CI, 1.1 to 2.3; P=0.004) and the response to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID (ICS step-up therapy) vs fluticasone 100 µg BID+montelukast 5 to 10 mg QD (LTRA step-up therapy)	while receiving fluticasone 100 µg BID		acute exacerbations, number of asthma control days, FEV_1 (one treatment period was ranked as better than another if the total amount of prednisone received during the period was ≤180 mg, if the number of annualized asthma-control days during the final 12 weeks of the period was increased by at least 31 days, or if the FEV_1 at the end of the period was at least 5% higher) Secondary: Not reported	ICS step-up (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to LABA step-up (P=0.009). White race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LTRA step-up (P=0.005). Secondary: Not reported
Gappa et al.[74] (2009) Salmeterol-fluticasone 50-100 µg BID (SFC) vs fluticasone 200 µg BID	DB, MC, PG, RCT Patients 6 to 14 years of age with persistent asthma uncontrolled by standard ICS doses	N=283 8 weeks	Primary: Change in mean morning PEF, asthma symptom scores, number of days without asthma symptoms, use of rescue albuterol, asthma control, and exacerbations	Primary: Mean increase in morning PEF was 30.4 L/min in SFC group and 16.7 L/min in fluticasone group. The mean improvement from baseline in morning PEF was significantly larger after SFC (8.6 L/min, 95% CI, 1.3 to infinity). Patients in the SFC group experienced more days without asthma symptoms (8.7%; 95% CI, 1.2 to 16.3) and more days without albuterol use (8.0%; 95% CI, 0.6 to 15.3) than patients receiving fluticasone. Good asthma control was achieved for a longer period in SFC group (3.4

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	weeks) than in the fluticasone group (2.7; P=0.02). Asthma exacerbations were recorded in three and six patients receiving SFC and fluticasone, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in two and one patients in the SFC and fluticasone groups, respectively. Secondary: Not reported
Lazarus et al.[75] (2001) Salmeterol 42 µg BID vs triamcinolone 400 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 to 65 years of age with persistent asthma	N=164 28 weeks	Primary: Change in AM PEF from the final week of the run in period to the final week of treatment Secondary: FEV_1, asthma symptom scores, rescue albuterol use, quality of life scores, and number of exacerbations	Primary: No significant difference in AM PEF measures was seen between the treatment groups; however, they were both more effective compared to placebo. Secondary: There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or quality of life; both treatment arms were more effective compared to placebo in these categories. There were significantly more group treatment failures in the salmeterol group than the triamcinolone (25 vs 6%; P=0.004) as well as more exacerbations (20 vs 7%; P=0.04).
Tattersfield et al.[76] (2001) Terbutaline 0.5 mg inhaled as needed vs formoterol 4.5 µg inhaled as needed	DB, PG, RCT Patients ≥18 years of age with asthma for at least six months who were treated with a constant dose of inhaled corticosteroid for at least 4 weeks	N=362 12 weeks	Primary: Time to first severe exacerbation Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication, and safety data	Primary: In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (P=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared with terbutaline group of 0.55. Secondary: No significant difference was seen between the treatment groups concerning daytime or nighttime symptoms. It was documented that pre bronchodilator FEV_1 was greater in the formoterol group than terbutaline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Both treatment groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40). Both treatments were well tolerated. Secondary: Not reported
Hermansson et al.[77] (1995) Terbutaline 500 µg QID vs salmeterol 50 µg BID	MC, OL, PG, RCT Patients ≥18 years of age with mild to moderate asthma	N=243 4 weeks	Primary: Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler, FEV_1 Secondary: Not reported	Primary: Salmeterol produced greater improvements than terbutaline in morning and evening PEF and diurnal variation (P<0.001, P=0.045, P<0.001, respectively). After four weeks, there was a significant difference in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (P<0.001, P=0.008, P=0.002, P=0.007) with salmeterol compared to terbutaline. After four weeks, there were no significant differences in FEV_1 or FVC between the two groups (P=0.598 and P=0.916, respectively). Secondary: Not reported
Hancox et al.[78] (1999) Terbutaline 1,000 µg QID vs budesonide 400 µg BID vs terbutaline 1,000	PC, RCT, XO Individuals aged 9 to 64 years of age with mild to moderate asthma with documented hyper-responsiveness	N=61 24 weeks	Primary: Construct a rank order of treatment from worst [1] to best [4], period of asthma control for each subject Secondary: PEF, nocturnal and daytime symptoms, use of rescue medication, and compliance	Primary: Combined treatment was ranked significantly higher than each individual treatment and placebo (P<0.0001, P<0.0001, and P<0.01), budesonide ranked higher than placebo (P=0.025), and there was no significant difference between budesonide and terbutaline or terbutaline and placebo. Secondary: Mean morning peak flow was higher during combined treatment than budesonide alone (P<0.02), and both the combined treatment and budesonide were higher than either placebo or terbutaline (P<0.01). Mean evening peak flow was higher with all treatments (P<0.0003) and was higher with the combined treatment than either active medication alone (P<0.0002), but no significant difference was seen between the two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg QID and budesonide 400 µg BID vs placebo				active medications alone. Nocturnal awakenings and percent of days during which wheeze was reported were reduced significantly in all treatment groups compared with placebo (P<0.0001, P<0.001), but did not differ significantly between the treatment groups. Rescue inhaler use significantly decreased (P<0.001) in all treatment groups compared with placebo, but did not differ significantly between the treatment groups. The self-reported compliance was above 90% for all groups and did not differ significantly.
Wechsler et al.[79] (2015) BELT LABA (salmeterol 50 µg or formoterol 9 µg, depending on the initial prescription by the treating physician) BID vs tiotropium 18 µg QD Each in addition to the patient's prior dose of ICS	MC, OL, PG, RCT Self-identified black patients 18 to 75 years of age with asthma who were receiving, or eligible for, step 3 or step 4 combination ICS and LABA therapy according to National Heart, Lung, and Blood Institute asthma guidelines	N=1070 6 to 18 months (mean of 310 days)	Primary: Time to first exacerbation Secondary: Patient-reported outcomes, FEV_1, rescue medication use, adverse events	Primary: There was no difference between LABA + ICS vs tiotropium + ICS in time to first exacerbation (mean number of exacerbations/person-year, 0.42 vs 0.37 (rate ratio, 0.90; 95% CI, 0.73 to 1.11; log-rank P=0.31). Secondary: Patient-reported outcomes scores all improved within both groups (P<0.001), but there was no difference between groups. There was also no between-group difference in change in lung function as measured by FEV_1 over the course of the entire study, nor at the 12-month time point (0.003 L for LABA + ICS vs −0.018 L for tiotropium + ICS; P=0.33) or 18-month time point (−0.053 L for LABA + ICS vs −0.078 L for tiotropium + ICS; P=0.49). There was no difference in average rescue medication use, which decreased when compared with baseline rescue medication use in both groups. The percentage of patients experiencing non–asthma-related or asthma-related adverse events and serious adverse events did not differ between treatments (2% of LABA + ICS patients vs 3% of tiotropium + ICS patients; P=0.16).
Chronic Obstructive Pulmonary Disease (COPD)				
Combivent Study Group[80] (1994)	DB, MC, PG, PRO, RCT	N=534 12 weeks	Primary: FEV_1, AUC, symptom score,	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (P<0.001 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albuterol 100 µg QID vs ipratropium 21 µg QID vs albuterol 100 µg and ipratropium 21 µg QID (fixed-dose combination MDI)	Patients ≥40 years of age with stable COPD		and safety Secondary: Not reported	P=0.015). There was no difference in symptom score between the groups. Compared with either agent alone, the overall FVC response was significantly greater in the combination group (P<0.01 to P=0.04). There were no significant differences between any of the treatment groups in terms of adverse effects or safety. Secondary: Not reported
Dorinsky et al.[81] (1999) Albuterol 180 µg QID vs ipratropium bromide 36 µg QID vs albuterol-ipratropium 180-36 µg QID	DB, MC, PG, RCT, RETRO Patients ≥40 years of age with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during the 3 months prior to the trials, FEV_1 ≤65% predicted value, and FEV_1 ≤70% of FVC	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as increase in FEV_1 of 12 and 15% from baseline) Secondary: Not reported	Primary: The percentage of patients demonstrating a 15 % increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the albuterol/ipratropium group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day 1 and 2 (of 4) (P<0.05). Overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from 2 to 8%. Significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in albuterol/ipratropium group compared to the individual treatment groups (P<0.05). Secondary: Not reported
Friedman et al.[82] (1999) Albuterol 180 µg	DB, MC, PG, RCT, RETRO Patients ≥40 years	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC from time 0	Primary: There was a significant improvement in FEV_1 in albuterol/ipratropium group compared to other treatment groups on all test days (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QID vs ipratropium bromide 36 µg QID vs albuterol-ipratropium 180-36 µg QID	of age with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during the 3 months prior to the trials, FEV_1 ≤65% predicted value, FEV_1 ≤70% of FVC		to four hours, total health care expenditures Secondary: Not reported	There was a significantly higher FEV_1 AUC_{0-4} in albuterol/ipratropium group compared to other treatment groups on all test days (P≤0.008). Secondary: Not reported
Tashkin et al.[83] (2007) Albuterol and ipratropium QID via nebulizer vs albuterol and ipratropium QID via inhaler vs albuterol and ipratropium nebulizer (morning and night) and MDI inhaler (afternoon and evening)	MC, PG, SB Patients >50 years of age with COPD, history of >10 pack-years of cigarette smoking, FEV1 >30% and <65% of predicted and a FEV_1 <70% of FVC	N=140 12 weeks	Primary: Quality of life and symptom sub-scores at 6 weeks and 12 weeks Secondary: Patient symptoms score, peak flow, and pre- and post-dose FEV_1	Primary: At 6 weeks, the total quality of life score was improved in the concomitant treatment group only (P=0.0196). Improvements in the symptoms sub-scores were seen in the nebulizer-only and concomitant treatment groups (P<0.019 and P<0.004, respectively). Improvement in the impacts sub-score was seen in the MDI inhaler-only group (P=0.0283). At 12 weeks, improvement in the symptoms sub-score was seen in the concomitant treatment group only (P=0.0186). Secondary: Changes in peak flow and pre-or post-bronchodilator FEV_1 were not significantly different between the treatment groups at six or 12 weeks. Patient symptom scores improved from baseline to week six and week 12 in the concomitant group (P<0.05), and at week 12 in the nebulizer-only group (P<0.05). There were no significant differences between the treatment groups.
Zuwallack et al.[84] (2010)	AC, DB, DD, MC, NI, PG, RCT	N=1,480	Primary: FEV_1 change from	Primary: On day 85, ipratropium-albuterol Respimat® inhaler was non inferior to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ipratropium-albuterol 20-100 µg QID, administered via Respimat® inhaler vs ipratropium-albuterol 36-206 µg QID, administered via aerosol MDI (Combivent®) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a 2 week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.	Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack years	12 weeks	test-day to baseline at day 85 for ipratropium-albuterol via Respimat® inhaler vs aerosol MDI and ipratropium-albuterol via Respimat® inhaler vs ipratropium via Respimat® inhaler Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC $AUC_{zero\ to\ six}$, $_{zero\ to\ four}$ and $_{four\ to\ six}$; peak FVC response on day one, 29, 57 and 85; safety	ipratropium-albuterol aerosol MDI at zero to six hours, and was "superior" to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium/albuterol Respimat® inhaler was non inferior to ipratropium Respimat® inhaler. Ipratropium-albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all test days. Secondary: Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium-albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium-albuterol Respimat® inhaler and ipratropium-albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium-albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium-albuterol aerosol MDI (172 to 219 minutes) overall. Median duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (n=358), 74 (n=357) and 63% (n=295) of patients receiving ipratropium-albuterol Respimat® inhaler, ipratropium-albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event was lower with ipratropium-albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium-albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium-albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
Baumgartner et al.[85] (2007) Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer	DB, DD, MC, PC RCT Patients ≥35 years of age with COPD	N=717 12 weeks	Primary: Pulmonary function Secondary: Dyspnea (Traditional Dyspnea Index); health status (St. George's Respiratory Questionnaire); adverse events; COPD exacerbations	Primary: Mean improvement in trough FEV_1 over 12 weeks was significantly greater with all three arformoterol doses (15 µg BID, 16.9%; 25 µg BID, 18.9%; 50 µg QD, 14.9%) and for salmeterol (17.4%) relative to placebo (6.0%; P<0.001). There were significantly greater improvements in the mean percentage change in FEV_1 $AUC_{0\text{-}12h}$ from the predose value over 12 weeks (15 µg BID, 12.7%; 25 µg BID, 13.9%; 50 µg QD, 18.9%; salmeterol, 9.8%) vs placebo (2.7%; P≤0.001). All doses of arformoterol were statistically different from salmeterol (P<0.024). Secondary: At week 12, TDI focal scores were significantly greater with all arformoterol doses compared with placebo (mean [95% CI]: 15 µg BID, 0.97 [0.25 to 1.69]; 25 µg BID, 1.08 [0.3 to 1.86]; 50 µg QD, 1.04 [0.32 to 1.771]), suggesting treatment-associated improvement in dyspnea;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol 42µg BID vs placebo				however, the difference between salmeterol and placebo was not statistically significant (0.36 [-0.40 to 1.12]). Improvements in health status, as measured using SGRQ total scores, were -2.6 to -3.6 U in the arformoterol groups, -4.4 U for salmeterol, and -1.2 U for placebo. The 95% CI of differences vs placebo suggested significant improvement for the arformoterol 25 µg BID and salmeterol groups. There was a similar frequency of AEs and COPD exacerbations across all groups.
Hanrahan et al.[86] (2008) Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer vs salmeterol 42 µg BID vs placebo	DB, RCT (pooled analysis of 2 trials) Patients ≥35 years of age with COPD	N=1,456 12 weeks	Primary: Percent change in trough FEV_1, percent change in FEV_1 average $AUC_{(0 - 12\ hrs)}$ and peak percent change FEV_1 from pre-dose Secondary: Not reported	Primary: Improvement in trough FEV_1 averaged over 12 weeks was greater for arformoterol and salmeterol compared to placebo (mean differences from placebo, arformoterol 15 µg BID: 11.4%; 25 µg BID: 15.4%; 50 µg daily: 10.9%; salmeterol: 11.6%). Greater improvements occurred after the first dose compared to placebo (mean differences between arformoterol and placebo for trough $FEV_{1:}$ 13 to 19%; FEV_1 $AUC_{(0 - 12\ hrs)}$: 19 to 24%; peak percent change: 20 to 25%) and at week 12 (trough FEV_1: 10 to 13%; FEV_1 $AUC_{(0 - 12\ hrs)}$: 6 to 13%; peak percent change: 7 to 14%). Increases in FEV_1 $AUC_{(0 - 12\ hrs)}$ and peak percent change were greater for arformoterol than for salmeterol (95% CI excluded zero). After 12 weeks, 78 to 87% of arformoterol subjects had ≥10% increases in FEV_1 from pre-dose (56% salmeterol, 44% placebo); the median time to response was three to 13 minutes (142 minutes salmeterol). Secondary: Not reported
Donohue et al.[87] (2014)	DB, MC, PC, RCT	N=841	Primary: Time from	Primary: Primary events were reported in 40 patients (9.5%) and 63 patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Arformoterol 15 µg BID vs placebo	Patients ≥40 years of age with COPD, smoking history ≥15 pack-years, FEV_1/FVC ≤70%, FEV_1 ≤65% predicted	1 year	randomization to respiratory death or first COPD exacerbation-related hospitalization Secondary: COPD exacerbations, mortality, adverse events	(15.0%) receiving arformoterol or placebo, respectively. Time to respiratory death or first COPD exacerbation-related hospitalization was 171.7 days and 155 days, respectively, for patients having a primary event. The point estimate for the primary event indicated an approximately 40% reduction in risk with arformoterol vs placebo (HR, 0.606; 90% repeated CI, 0.425 to 0.864). Secondary: Risks for first protocol-defined COPD exacerbation (HR, 0.801; P=0.078) and recurrent protocol-defined COPD exacerbation (HR, 0.768; P=0.043) were lower with arformoterol than placebo. Patients receiving arformoterol or placebo had a similar incidence of adverse events (72.9 vs 68.2%, respectively). Twelve patients (2.9%) receiving arformoterol and 10 patients (2.4%) receiving placebo died postrandomization.
Donohue et al.[88] (2008) Arformoterol 50 µg QD vs salmeterol 42 µg BID	MC, OL, RCT Patients with COPD	N=793 12 months	Primary: Adverse events, COPD exacerbations, use of short-acting bronchodilators, and pulmonary function Secondary: Not reported	Primary: The frequency of adverse events was similar for those taking arformoterol (90.5%) and salmeterol (88.3%). Tremor was more frequent among patients treated with arformoterol (13.4%) than those treated with salmeterol (1.1%). The frequency of COPD exacerbations did not increase over 12 months for arformoterol and salmeterol (weeks 0 to 13: 15.7 and 11.7%, respectively; weeks 39 to 52: 10.0 and 9.4%, respectively). Supplemental ipratropium bromide and albuterol use decreased for both groups by 0.8 to 1.5 actuations/day. Mean predose FEV_1 improved for arformoterol and salmeterol at week 13 (7.1 and 7.6%, respectively), and the improvement continued at week 52 (5.9 and 6.2%, respectively). Mean peak percent predicted postdose FEV_1 declined by about 2% for both treatments over the course of the 52-week study, but was higher for arformoterol than for salmeterol.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Tashkin et al.[89] (2009) Arformoterol 15 µg BID vs tiotropium 18 µg QD vs arformoterol 15 µg BID and tiotropium 18 µg QD	MB, MC, PG, RCT Patients ≥45 years of age with COPD, smoking history ≥15 pack-years, breathless severity ≥2 on Medical Council Dyspnea Score, pre bronchodilator FEV_1 >0.7, FEV_1/FVC ≤70%, FEV_1 ≤65% predicted	N=234 2 weeks	Primary: Difference in mean FEV_1 AUC_{0-24} Secondary: Differences in rescue therapy use and occurrence of adverse events	Primary: Mean FEV_1 AUC_{0-24} improved to a similar degree with arformoterol (0.10 L) and tiotropium (0.08 L), and was greater with combination therapy (0.22 L; all P<0.005). Peak FEV_1, peak FVC, 24-h trough FEV_1, and inspiratory capacity also improved to a similar degree with arformoterol and tiotropium, and were greatest with combination therapy. Dyspnea (mean transition dyspnea index) improved to a similar degree with arformoterol (2.3) and tiotropium (1.8), and was greatest with combination therapy (3.1; all P<0.05). Secondary: Levalbuterol use decreased for all treatment groups (range -1.8 to -2.5 actuations per day). All treatments had similar overall frequencies of adverse events: arformoterol (25.0%), tiotropium (27.5%) and combination (30.8%).
Benhamou et al.[90] (2001) Formoterol 24 µg inhaled via dry powder inhaler (1 dose) vs albuterol 400 µg inhaled via dry powder inhaler (1 dose)	DB, PC, RCT, XO Patients 40 to 75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (0-30 min) of FEV_1 in one minute Secondary: AUC (0-1 hour) of FEV_1 in one minute, AUC (0-3 hours) of FEV_1 in one minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (-0.32; P<0.0001). Secondary: There were no statistical differences between the two active medication groups in secondary endpoints, and each had a similar onset (five minutes). No serious adverse effects or clinically relevant changes in vital sign were observed in any of the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Cazzola et al.[91] (2002) Formoterol 12 µg, 12 µg, and 24 µg vs albuterol metered dose inhaler (MDI) 200 µg, 200 µg, and 400 µg Doses were administered on two consecutive days.	RCT, SB, XO Patients 51 to 77 years of age with COPD who had an acute exacerbation (defined as sustained worsening of the patient's condition from stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen)	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary: Spirometric data (inspiratory capacity and FVC), pulse rate, SpO_2 values	Primary: There was a significant increase in FEV_1, inspiratory capacity, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol ($P<0.05$). Secondary: There was no significant difference between FEV_1, inspiratory capacity, and FVC values in the formoterol group compared to the albuterol group after 48 µg of formoterol and 800 µg of albuterol. There was a significant increase in change in FEV_1 values after 24 µg of formoterol compared to 48 µg of formoterol ($P=0.022$). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 µg of formoterol or 800 µg of albuterol ($P>0.05$). SpO_2 values decreased below 90% in two patients after the highest dose of formoterol and in 1 patient after the highest dose of albuterol. The clinical significance of was not reported.
Donohue et al.[92] (2008) Formoterol 20 µg BID via nebulizer (FFIS) vs formoterol 12 µg BID via dry powder inhaler (FA)	AC, ES, OL Patients ≥40 years of age with COPD who were current or former smokers	N=569 12 months	Primary: Safety Secondary: Not reported	Primary: A total of 73% of FFIS-treated patients and 78% of FA-treated patients experienced an adverse event over the course of the study. The majority of were mild to moderate and considered unrelated to treatment. COPD exacerbation occurred in 15.8% of FFIS-treated and 17.9% of FA-treated patients. Deaths, serious adverse events, and discontinuations for adverse events occurred in 1.3, 16.2, and 5.4% of the nebulized group vs 1.9, 17.9, and 7.5% of the inhaled group, respectively. There were no clinically significant changes from baseline in any laboratory parameters.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Hanania et al.[93] (2018) Formoterol fumarate 20 µg inhalation solution BID (Perforomist®) vs placebo	DB, MC, NI, RCT Patients ≥40 years of age with COPD who had experienced ≥1 COPD exacerbations within the past year, smoking history >10 pack-years, FEV_1/FVC ≤70%, FEV_1 30 to 70% predicted	N=1,071 1 year	Primary: The combined incidence of respiratory death, first COPD-related ER visit, or first COPD exacerbation-related hospitalization Secondary: Safety and tolerability	Primary: Among 1,071 randomized patients, 121 had ≥1 primary end point events (formoterol, 11.8%; placebo, 10.8%). The Kaplan–Meier estimate of the cumulative probability of a primary end point event at week 52 was 15.5% in the formoterol group and 14.9% in the placebo group, with an estimated HR of formoterol to placebo of 0.965 (90% CI, 0.711 to 1.308), demonstrating that formoterol was noninferior to placebo. Secondary: No respiratory-related deaths occurred in the FFIS-treated group, and one respiratory-related death (COPD) occurred in the placebo group. A total of 148 (27.4%) subjects in the FFIS group and 138 (26.0%) subjects in the placebo group had at least one protocol-defined COPD exacerbation recorded. The cumulative probabilities of an event at Week 52 were similar (34.7% for the FFIS group vs 34.0% for the placebo group). While the percentage of patients with COPD exacerbations was comparable between the FFIS and placebo groups, the time to the first exacerbation was longer for FFIS compared with that for placebo, with the time at which at least 30% of patients had an event estimated as 43.3 and 36.9 weeks, respectively. Adverse events were similar for formoterol vs placebo (patients with ≥1 treatment-emergent adverse events: 69.1% vs 69.6%, respectively). Improvements from baseline in spirometry end points were all numerically greater in the formoterol group compared with the placebo group at all visits during the study. Estimated differences (formoterol–placebo) in the improvements were statistically significant for FEV_1 (3- and 6-month visits; $P<0.05$), FVC (all visits; $P<0.005$), and % predicted FEV_1 (3-, 6-, and 9-month visits; $P<0.05$).
Bouros et al.[94] (2004) Formoterol 12 to 24 µg	MC, PC, RCT, XO Patients with stage II and III COPD who demonstrated	N=47 Single dose	Primary: Inspiratory capacity (IC) measured before dosing and at five,	Primary: Both formoterol and salmeterol increase inspiratory capacity in patients with COPD. Formoterol 12 µg was significantly more effective than salmeterol 50 µg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs salmeterol 50 to 100 µg vs placebo	an increase in FEV_1 of ≤12% from the patient's predicted normal value after salbutamol inhalation		10, 15 and 30 minutes and one, two, three and four hour post-dose Secondary: Not reported	during the first hour post-dose as indicated by notable differences at all times during the first hour post-dose. Secondary: Not reported
Cote et al.[95] (2009) Formoterol 12 µg BID vs salmeterol 50 µg BID	MC, OL, PG, RCT Patients ≥40 years of age with COPD who were current or former smokers	N=270 28 days	Primary: Pulmonary function, changes in baseline in the six minute walk test, rescue medication use, and safety assessments Secondary: Not reported	Primary: Change from baseline in FEV_1 at five minutes postdose on day 28 was 0.13 L in the formoterol group compared with 0.07 L in the salmeterol group (P=0.022). At 30 minutes postdose on day 28, the change from baseline in FEV_1 was 0.17 L in the formoterol group compared with 0.07 L in the salmeterol group (P<0.001). Similar changes were reported at 60 min post-dose. There was no significant difference in walking distance or use of rescue medication between the treatment groups. Treatment-emergent adverse events were generally mild-to-moderate in both groups, with 25.5% reported in the formoterol group and 17.3% reported in the salmeterol group (P=0.105). Treatment-associated adverse events were observed in 5.8% of patients in the formoterol group and 1.5% of patients in the salmeterol group (P=0.103). Secondary: Not reported
Berton et al.[96] (2010) Formoterol 12 µg BID plus tiotropium 18 µg	DB, XO Patients with moderate to severe COPD	N=33 2 weeks	Primary: Change in inspiratory capacity, obtained on constant-speed treadmill tests to	Primary: FOR-TIO was more effective than FOR-PLA in increasing post-treatment FEV_1 and limit of tolerance (1.34 vs 1.25 L and 124 vs 68, respectively; P<0.05). FOR-TIO slowed the rate of decline in exercise inspiratory capacity

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD (FOR-TIO) vs formoterol 12 µg BID plus placebo (FOR-PLA)			the limit of tolerance Secondary: Not reported	compared to FOR-PLA (Δ isotime-res, -0.27 vs -0.45 L; P<0.05). End-expiratory lung volume (percent total lung capacity) was further reduced with FOR-TIO (P<0.05). Improvement in Tlim with FOR-TIO was also related to larger increases in FEV_1 (P<0.05). Secondary: Not reported
Van Noord et al.[97] (2005) Formoterol 12 µg BID for 6 weeks vs tiotropium 18 µg QD for 6 weeks vs tiotropium 18 µg QD and formoterol 12 µg BID for 6 weeks	DB, RCT, XO Patients with COPD	N=71 18 weeks	Primary: FEV_1, FVC, rescue medication use Secondary: Not reported	Primary: Tiotropium produced a significantly greater improvement in average daytime FEV_1 (0 to 12 h) than formoterol (127 vs 86 mL). The average nighttime FEV_1 (12 to 24 h) was not different among the treatment groups (tiotropium 43 mL and formoterol 38 mL). Combination therapy had significantly greater improvements in both endpoints compared to monotherapy (daytime 234 mL and nighttime 86 mL). Changes in FVC were similar to the changes in FEV_1 results. Daytime salbutamol use was significantly lower with combination therapy compared to monotherapy (tiotropium plus formoterol 1.81 puffs/day, tiotropium 2.41 puffs/day, formoterol 2.37 puffs/day). Secondary: Not reported
Ferguson et al.[98] (2017) RISE Budesonide/ formoterol 320/9 µg BID pressurized metered-dose inhaler	DB, DD, MC, RCT Patients ≥40 years of age with moderate-to-very-severe COPD and a history of ≥1 COPD exacerbation within a year before screening and a	N=1,219 6 months	Primary: Annual rate of COPD exacerbations Secondary: Time to first exacerbation, change from baseline in for	Primary: Budesonide/formoterol resulted in a 24% reduction in annual rate of exacerbations (0.85 vs 1.12; rate ratio, 0.76; 95% CI, 0.62 to 0.92; P=0.006). Secondary: Time to first exacerbation showed a reduction in risk of 22% with budesonide/formoterol versus formoterol (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.0164). Budesonide/formoterol treatment resulted in a statistically significant difference in predose FEV_1 (P=0.0091)) and reduction in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs formoterol 9 µg BID dry powder inhaler	smoking history of ≥10 pack years		predose FEV_1, SGRQ score, nighttime awakenings due to COPD, safety	percentage of nighttime awakenings from baseline to treatment average (P=0.0048) compared with formoterol. SGRQ score was improved in patients treated with budesonide/formoterol vs formoterol (P=0.0070). The most commonly reported adverse events (≥3%) in budesonide/formoterol and formoterol groups were COPD (4.5% vs 8.6%) and nasopharyngitis (5.0% vs 5.2%). Pneumonia adverse events were reported in 0.5% and 1.0% of budesonide/formoterol-treated and formoterol-treated patients, respectively.
Martinez et al.[99] (2017) PINNACLE-1 and PINNACLE-2 Glycopyrrolate-formoterol 18-9.6 µg BID vs glycopyrrolate 18 µg BID vs formoterol 9.6 µg BID vs placebo BID or tiotropium 18 µg QD (OL comparator in PINNACLE-1 only)	DB, MC, PC, RCT Patients 40 to 80 years of age with moderate-to-very severe COPD, a smoking history of at least 10 pack-years, and a postbronchodilator FEV_1/FVC ratio <0.70 and FEV_1 <80% predicted	N=2,103 (PINNACLE-1) N=3,125 (PINNACLE-2) 24 weeks	Primary: Change from baseline in morning predose trough FEV_1 at week 24 Secondary: Change from baseline in morning predose trough FEV_1 over 24 weeks, peak change from baseline in FEV_1 within two hours postdose at week 24, time to onset of action on day one, change from baseline in SGRQ total score, and change from baseline in average daily rescue albuterol use	Primary: At week 24, differences in change from baseline in the morning predose trough FEV_1 for glycopyrrolate-formoterol vs placebo, glycopyrrolate, and formoterol were 150 mL, 59 mL, and 64 mL in PINNACLE-1 (all P<0.0001) and 103 mL, 54 mL, and 56 mL in PINNACLE-2 (all P<0.001), respectively. Secondary: The change from baseline in morning predose trough FEV_1 over 24 weeks was similar but with slightly larger estimated differences vs placebo. For peak change from baseline in FEV_1 within two hours postdose at week 24, glycopyrrolate-formoterol showed significant differences vs placebo and monocomponents in both PINNACLE-1 and PINNACLE-2 (all P<0.0001). The change from baseline in peak FEV_1 within two hours postdose over 24 weeks was similar. For onset of action on day one, glycopyrrolate-formoterol showed a significant difference from placebo at five minutes, which was the first time point assessed in both studies, with respective differences of 187 mL and 186 mL (all P<0.0001). In PINNACLE-1 only, glycopyrrolate-formoterol showed significant differences in SGRQ total score at week 24 vs placebo (–2.52) and glycopyrrolate MDIs (–2.33). Glycopyrrolate-formoterol-treated patients were more likely to achieve the minimum clinically important difference of 4 units in SGRQ total score vs glycopyrrolate and placebo in PINNACLE-1 (all P<0.05). In PINNACLE-1 and PINNACLE-2, glycopyrrolate-formoterol showed a significant reduction in rescue albuterol use over 24 weeks vs placebo (–1.08 and –1.04 puffs/day,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively). In PINNACLE-2, a significant reduction vs glycopyrrolate (–0.57) was seen, with nominal significance vs formoterol (–0.29).
Lipworth et al.[100] (2018) PINNACLE-4 Glycopyrrolate-formoterol 18-9.6 µg BID vs glycopyrrolate 18 µg BID vs formoterol 9.6 µg BID vs placebo BID	DB, MC, PC, RCT Patients 40 to 80 years of age with moderate-to-very severe COPD, a smoking history of at least 10 pack-years, and a postbronchodilator FEV_1/FVC ratio <0.70 and FEV_1 <80% predicted	N=1,740 24 weeks	Primary: Change from baseline in morning predose trough FEV_1 at week 24 Secondary: Change from baseline in morning predose trough FEV_1 over 24 weeks, peak change from baseline in FEV_1 within two hours postdose at week 24, time to onset of action on day one, change from baseline in SGRQ total score, and change from baseline in average daily rescue medication use	Primary: Treatment with glycopyrrolate-formoterol resulted in greater improvements in change in trough FEV_1 vs placebo (least squares mean [LSM] difference, 165 mL; P<0.0001), glycopyrrolate (LSM difference, 59 mL; P<0.0001), and formoterol (LSM difference, 72 mL; P<0.0001). Glycopyrrolate and formoterol treatments significantly increased morning predose trough FEV_1 at Week 24 compared to placebo (LSM difference, 105 and 92 mL, respectively; both P<0.0001). Secondary: Similar improvements as for the primary endpoint were observed for change from baseline in morning predose trough FEV_1 over 24 weeks. Glycopyrrolate-formoterol led to significant improvements in peak change from baseline in FEV_1 within two hours postdose at Week 24 compared to glycopyrrolate, formoterol, and placebo. Onset of action for glycopyrrolate-formoterol, glycopyrrolate, and formoterol occurred within five minutes postdose (LSM differences vs placebo, 179 mL, P<0.0001; 37 mL, P=0.0002; and 164 mL, P<0.0001, respectively). Improvements in rescue medication use were observed for glycopyrrolate-formoterol vs glycopyrrolate (LSM difference, -0.77; P=0.0001) and placebo in the rescue medication user population (LSM difference, -0.98; P<0.0001).
Singh et al.[101] (2014) ACLIFORM-COPD Aclidinium/ formoterol 400/12 µg BID	DB, MC, RCT Patients ≥40 years of age with a smoking history ≥10 pack-years, post-bronchodilator FEV_1/FVC <70%, and FEV_1 ≥30% but	N=1,729 24 weeks	Primary: Co-primary endpoints were change from baseline at Week 24 in 1-hour morning post-dose FEV_1 versus aclidinium and	Primary: At Week 24, aclidinium/formoterol 400/12 µg and 400/6 µg lead to improvements from baseline in 1-hour post-dose FEV_1 versus aclidinium (125 mL; 95% CI, 90 to 160; P<0.001; and 69 mL; 95% CI, 34 to 105; P<0.001, respectively) and trough FEV_1 versus formoterol (85 mL; 95% CI, 51 to 119; P<0.001; and 53 mL; 95% CI, 19 to 87; P<0.01, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aclidinium/ formoterol 400/6 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID vs placebo BID	<80% predicted normal		morning pre-dose (trough) FEV_1 versus formoterol Secondary: TDI focal score and change from baseline in SGRQ total score at Week 24 (both versus placebo)	At Week 24, both fixed-dose combination doses caused clinically significant improvements (≥1 unit) in TDI focal score versus placebo (400/12 µg, 1.29 units; and 400/6 µg, 1.16 units; both P<0.001). Aclidinium and formoterol monotherapies caused significant improvements (both P<0.005) versus placebo at Week 24 that fell just below the 1-unit threshold. At Week 24, all active treatments were associated with improvements in mean SGRQ total score >4 units; however, there was a very high placebo response and there were no statistically significant differences between active and placebo treatments.
D'Urzo et al.[102] (2014) AUGMENT COPD Aclidinium/ formoterol 400/12 µg BID vs aclidinium/ formoterol 400/6 µg BID vs aclidinium 400 µg	DB, MC, RCT Patients ≥40 years of age with a smoking history ≥10 pack-years, post-bronchodilator FEV_1/FVC <70%, and FEV_1 ≥30% but <80% predicted normal	N=1,692 24 weeks	Primary: Co-primary endpoints were change from baseline at Week 24 in 1-hour morning post-dose FEV_1 versus aclidinium and morning pre-dose (trough) FEV_1 versus formoterol Secondary: TDI focal score and change from baseline in SGRQ total score at Week	Primary: Improvements from baseline in 1-hour postdose FEV_1 were greater in patients treated with aclidinium/formoterol 400/12 µg or 400/6 µg compared with aclidinium (108 mL and 87 mL, respectively; P<0.0001). Improvements in trough FEV_1 were greater in patients treated with aclidinium/formoterol 400/12 µg versus formoterol (45 mL; P=0.0102), a numerical improvement of 26 mL in trough FEV_1 over formoterol was observed with aclidinium/formoterol 400/6 µg. Secondary: At week 24, improvements in TDI focal scores were achieved with the aclidinium/formoterol fixed-dose combinations compared with placebo (P<0.0001), as well as with either aclidinium or formoterol (P≤0.01 for both versus placebo). Treatment with the aclidinium/formoterol combinations resulted in numerically greater improvements in TDI focal scores compared to either monotherapy. At week 24, improvements in SGRQ total scores from baseline were observed with the aclidinium/formoterol combinations and the monotherapies versus placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs formoterol 12 µg BID vs placebo BID			24 (both versus placebo)	(P<0.05). At all timepoints, a greater percentage of responders (patients achieving ≥4-unit improvement from baseline in SGRQ total score) were observed with either aclidinium/formoterol combination versus placebo, including at study end (both P<0.01).
Sethi et al.[103] (2019) AMPLIFY Aclidinium/ formoterol 400/12 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID vs tiotropium 18 µg once daily	AC, DB, MC, RCT Patients ≥40 years of age with a smoking history ≥10 pack-years, post-bronchodilator FEV_1/FVC <70%, and FEV_1 <80% predicted normal	N=1,594 24 weeks	Primary: Co-primary endpoints were change from baseline at Week 24 in 1-hour morning post-dose FEV_1 versus aclidinium and morning pre-dose (trough) FEV_1 versus formoterol Secondary: Change from baseline in normalized $AUC_{0–3/h}$ FEV_1, proportion of SGRQ total score responders (≥4-unit improvement)	Primary: Treatment with aclidinium/formoterol resulted in greater improvements in 1-hour post-dose FEV_1 compared with aclidinium (84 mL, P<0.0001), formoterol (84 mL, P<0.0001), and tiotropium (92 mL, P<0.0001). Aclidinium/formoterol led to significantly greater improvements in change from baseline in morning pre-dose (trough) FEV_1 vs formoterol (55 mL, P<0.001); however, the improvements for aclidinium/formoterol compared with aclidinium (14 mL) and tiotropium (19 mL) did not reach statistical significance. Secondary: On day one and at week 24, there were significantly greater improvements from baseline in $AUC_{0–3/h}$ FEV_1 with aclidinium/formoterol compared with aclidinium, formoterol, or tiotropium. Aclidinium/formoterol, aclidinium, and tiotropium improved SGRQ total score vs baseline by more than ≥4 units at week 24 (4.68, 4.95, and 5.58 units, respectively). Formoterol improved SGRQ by 3.96 units compared with baseline. There were no significant differences between treatments in the proportion of SGRQ responders (48.1%, 49.1%, 49.6%, and 50.6% for aclidinium/formoterol, aclidinium, formoterol, and tiotropium, respectively)
Vogelmeier et al.[104] (2016) AFFIRM COPD	AC, DB, MC, RCT Patients ≥40 years of age with a smoking history	N=933 24 weeks	Primary: Peak FEV_1 at week 24 Secondary:	Primary: Peak FEV_1 was greater with aclidinium/formoterol versus salmeterol/fluticasone at week 24, with significant differences observed after the first dose on day one and at all intervening time-points (all P<0.0001)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aclidinium/ formoterol 400/12 µg BID vs salmeterol/ fluticasone 50/500 µg BID	≥10 pack-years, post-bronchodilator FEV_1/FVC <70%, and FEV_1 <80% predicted normal		TDI focal score, TDI and SGRQ responders, exacerbations, use of reliever medication	Secondary: Noninferiority of aclidinium/formoterol versus salmeterol/fluticasone in TDI focal score was demonstrated at week 24 (95% CI, −0.46 to 0.46), as well as at week four (95% CI, −0.34 to 0.40) and week 12 (95% CI, −0.43 to 0.39). At week 24, 55.6% of patients in the aclidinium/formoterol group and 54.5% in the salmeterol/fluticasone group achieved improvements in TDI greater than the minimum clinically important difference (≥1 unit). Mean improvements in SGRQ total scores at week 24 were similar following treatment with aclidinium/formoterol or salmeterol/fluticasone (−4.7 and −5.7, respectively; P=0.27). At week 24, 52.6% of patients in the aclidinium/formoterol group and 55.8% in the salmeterol/fluticasone group achieved improvements from baseline in SGRQ total scores greater than the minimum clinically important difference (≥4 units). There were no significant differences in the incidence of exacerbations between the aclidinium/formoterol and salmeterol/fluticasone groups. There was no significant difference between groups in the use of relief medication (both 0.9 puffs per day at week 24).
Ikeda et al.[105] (1995) Ipratropium 40 µg plus albuterol 200 µg vs ipratropium 80 µg plus albuterol 400 µg vs ipratropium 40 µg vs	DB, PC, RCT, XO Adult male patients with stable COPD	N=26 1 month	Primary: FEV_1, FVC, and adverse reactions Secondary: Not reported	Primary: All treatments led to a significant improvement in FEV_1 and FVC compared to placebo (P<0.01). Treatment with ipratropium/albuterol 80/400 µg led to significantly greater improvements in FEV_1 compared to other treatment groups (P<0.05). Low-dose ipratropium/albuterol led to significant improvements in FVC compared to low-dose ipratropium (P<0.01), but not high-dose ipratropium (P=NS). No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ipratropium 80 µg vs placebo				
Datta et al.[106] (2003) Levalbuterol 1.25 mg via nebulizer vs albuterol 2.5 mg via nebulizer vs albuterol 2.5 mg combined with ipratropium 0.5 mg via nebulizer vs placebo	DB, RCT, XO Patients with COPD (mean age of 69 years), FEV_1 45 to 75% of predicted value, FEV_1/FVC ratio of <0.70, stable disease (absence of clinical exacerbation and no change in COPD medications in previous month)	N=30 4 days	Primary: FEV_1 Secondary: FVC, pulse rate, oxygen saturation (measured by pulse oximetry), hand tremor (rating scale 0 to 7, rated by same blinded investigator for all patients) Secondary: Not reported	Primary: Mean change in FEV_1 from baseline increased significantly in all three active treatment groups compared to placebo at 0.5 hours and persisted at one hour (P<0.05). At two hours, only the combined albuterol and ipratropium group had a mean change in FEV_1 that was significantly better than placebo (P=0.04). This effect persisted at three hours for the combined albuterol and ipratropium group (P<0.05). There were no significant differences between active treatment groups at any time during the study. The percentage of patients in exhibiting a positive bronchodilator response (defined as both a >12% increase and a 0.20 liter increase in FEV_1) was significantly increased in all three active treatment groups compared to placebo at 0.5 hours ($P \leq 0.03$) and this persisted at one hour ($P \leq 0.03$). The percentage of patients in exhibiting a positive bronchodilator response at two and three hours was only significant compared to placebo in the combined albuterol and ipratropium group (P=0.03 at two hours and P=0.003 at three hours). Between-group comparisons were not reported. Secondary: All three active treatment groups led to significant improvements in FVC compared to placebo at 0.5 hours (P<0.05) and remained significant at one hour only for the combined albuterol and ipratropium group (P<0.05). No significant differences between active treatment groups and placebo were noted from two hours on. Differences in FVC between active treatment groups were similar. Significant increases in pulse rate compared to placebo were noted at 0.5 hours in the albuterol and levalbuterol groups (P<0.01) but no differences were noted at one hour and beyond.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant changes in oxygen saturation were noted in any group compared to placebo. No significant differences in hand tremor noted between groups.
Donohue et al.[107] (2006) Levalbuterol (LEV) 0.63 mg or 1.25 mg TID via nebulizer vs albuterol (RAC) 2.5 mg TID via nebulizer vs placebo	DB, MC, PG, RCT Adults with COPD	N=209 6 weeks	Primary: Average FEV_1 $AUC_{(0\text{-}8\ hrs)}$ over weeks 0, two and six, rescue medication use, safety parameters, COPD exacerbations, and global evaluations Secondary: Not reported	Primary: All active treatments demonstrated improvements in the percent change in FEV_1 $AUC_{(0\text{-}8\ hrs)}$ during the DB period and at each visit compared to placebo ($P<0.05$). Rescue medication use vs baseline (doses/day) changed over time: placebo +0.38; LEV 0.63 mg +0.07; LEV 1.25 mg -0.84 ($P=0.02$ vs RAC); RAC +0.97. The overall rate of adverse events was 56.4% for placebo, 56.6% for LEV 0.63 mg, 67.3% for LEV 1.25 mg, and 65.4% for RAC. COPD exacerbations occurred in all groups (placebo 12.7%, LEV 0.63 mg 11.3%; LEV 1.25 mg 18.4%; RAC 21.2%). Withdrawals due to COPD exacerbations were significantly higher in the RAC group compared with placebo (PBO 0%; LEV 0.63 mg 1.9%; LEV 1.25 mg 4.1%; RAC 9.6% ($P=0.01$ vs placebo). Secondary: Not reported
Koch et al.[108] (2014) Olodaterol 5 µg QD vs olodaterol 10 µg QD	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤80% predicted and FEV_1/FVC ≤70%	N=1,838 48 weeks	Primary: FEV_1 area under the curve from 0 to 3 hours ($AUC_{0–3}$), trough FEV_1 response after 24 weeks of treatment, TDI all at 24 weeks Secondary:	Primary: After 24 weeks, statistically significant improvements in FEV_1 $AUC_{0–3}$ response ($P<0.0001$) and trough FEV_1 response ($P<0.01$) were demonstrated with olodaterol 5 µg, olodaterol 10 µg, and formoterol vs placebo. After 24 weeks' treatment, the analysis revealed no statistically significant differences in TDI focal score for any of the active therapies vs placebo. Secondary: Secondary lung-function responses over 48 weeks of treatment were in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs formoterol 12 µg BID vs placebo			SGRQ, additional FEV_1 and FVC parameters	line with the primary end points. Combined analysis of SGRQ after 24 weeks illustrated an improvement in total score for olodaterol 5 µg (−2.8 difference from placebo; P<0.005) and olodaterol 10 µg (−3.4 difference from placebo; P<0.0005), but not formoterol (−1.2; P= not significant) compared to placebo.
Ferguson et al.[109] (2014) Olodaterol 5 µg QD vs olodaterol 10 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤80% predicted and FEV_1/FVC ≤70%	N=1,266 48 weeks	Primary: FEV_1 area under the curve from 0 to 3 hours ($AUC_{0–3}$), trough FEV_1 response after 24 weeks of treatment, rescue medication use, all at 12 weeks Secondary: Additional FEV_1 and FVC parameters, safety	Primary: After 12 weeks, statistically significant improvements compared with placebo were demonstrated in the end point of FEV_1 $AUC_{0–3}$ response for both olodaterol 5 µg and 10 µg once daily (P<0.0001). Statistically significant improvements vs placebo in trough FEV_1 response was also observed. Weekly mean daytime and nighttime rescue medication use with olodaterol was significantly reduced vs placebo over the 48 weeks of treatment; at week 48, daytime rescue medication use was reduced for olodaterol 5 µg by 0.46 actuations/day (P<0.0001) and for 10 µg by 0.57 actuations/day (P<0.0001); night-time rescue medication use was reduced for olodaterol 5 µg by 0.50 actuations/day (P<0.0001) and for 10 µg by 0.78 actuations/day (P<0.0001). Secondary: Over the 48-week treatment period, the FEV_1 $AUC_{0–3}$ response with olodaterol 5 µg and 10 µg once daily was significantly improved compared with placebo at all time points (P<0.0001). In both studies, the incidences of adverse events, serious adverse events, deaths, and adverse events leading to discontinuations with olodaterol 5 µg and 10 µg once daily were similar to those for placebo.
Hanania et al.[110] (2003) Salmeterol 50 µg BID	DB, MC, PC, RCT Patients 40 to 87 years of age with COPD, current or former smokers	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and two-hour post-dose FEV_1 Secondary:	Primary: There was a significant increase in pre-dose FEV_1 in the fluticasone-salmeterol group compared to the salmeterol group (P=0.012) and placebo (P<0.001). There was no significant difference between the fluticasone-salmeterol group and the fluticasone group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone 250 µg BID vs fluticasone-salmeterol 250-50 µg BID vs placebo	with ≥20 pack-year history, FEV_1/FVC ratio of ≤70%, baseline, FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)		Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire, chronic bronchitis symptom questionnaire, exacerbations, and supplemental albuterol use	There was a significant increase in 2-hour post-dose FEV_1 in the fluticasone-salmeterol group compared to the salmeterol group (P<0.001), placebo (P<0.001), and fluticasone group (P≤0.048). Secondary: There was a significant increase in the morning PEF values in the fluticasone-salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (P≤0.034), though improvements were also seen from baseline in salmeterol and fluticasone monotherapy groups (P<0.001). There was a significant improvement in the dyspnea index observed in fluticasone-salmeterol group (P=0.023) compared to placebo, in addition to improvements in fluticasone (P=0.057) and salmeterol (P=0.043) monotherapy groups compared to placebo (NOTE: difference in fluticasone monotherapy group not significant). There was a significant reduction in supplemental albuterol use in the fluticasone-salmeterol group compared to the fluticasone monotherapy group (P=0.036) and placebo (P=0.002). There was a numerical reduction in supplemental albuterol use in the fluticasone-salmeterol group compared to salmeterol monotherapy group. There was a significant increase in chronic respiratory disease questionnaire scores in the fluticasone-salmeterol group compared to placebo (P=0.006). There was a significant increase in chronic respiratory disease questionnaire scores in fluticasone monotherapy group compared to placebo (P=0.002). There was a significant increase in chronic bronchitis symptom questionnaire scores in fluticasone-salmeterol group and fluticasone monotherapy group compared to placebo (P≤0.017).
Matera et al.[111] (1996) Salmeterol 50 µg BID and ipratropium	SB, RCT, XO Male patients ≥40 years of age with COPD and FEV_1 between 16 and	N=12 4 days	Primary: Changes in FEV_1 and changes in the area under the FEV_1 response-time curve (AUC)	Primary: The peak response for salmeterol (28.8%) was greater than that for ipratropium (26.0%). Equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0%). All active treatments produced a significant bronchodilation effect from 15

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 µg QID vs ipratropium 40 µg QID vs salmeterol 50 µg BID vs placebo	62% of predicted value		Secondary: Not reported	to 360 minutes when compared to placebo (P=0.05). Only salmeterol and salmeterol plus ipratropium induced a significant spirometric increase over the 12 hour monitoring period (P=0.05). All of the AUC values for active treatments were significantly greater than for placebo (P=0.05). The AUC values for salmeterol and salmeterol plus ipratropium were significantly greater than for ipratropium alone (P=0.05). There was no significant difference between the salmeterol and salmeterol plus ipratropium AUC (P>0.05). Secondary: Not reported
Van Noord et al.[112] (2000) Salmeterol 50 µg BID and ipratropium 40 µg QID vs salmeterol 50 µg BID vs placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with COPD and FEV_1 $\leq$75% predicted	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication used, PEF, clinic lung function, adverse events, exacerbations	Primary: Treatment with salmeterol led to a mean peak increase in FEV_1 of 7% predicted after two hours, followed by a plateau. After 12 hours, the improvement was 2% of predicted. Salmeterol plus ipratropium produced a peak increase in FEV_1 of 11% predicted after two hours. After 12 hours, the improvement was 3% predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary: Throughout the treatment period there was a mean decrease in the daytime symptom score from 1.9 to 1.7 in the placebo group (P=NS), 2.0 to 1.4 (P=0.001) in the salmeterol group and 2.0 to 1.3 (P=0.001) in the salmeterol plus ipratropium group. Compared with placebo, treatment with salmeterol and salmeterol plus ipratropium was associated with a higher percentage of days and nights without the use of additional albuterol (P=0.01). No difference was observed between the two active treatment groups (P=0.35). Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (P=0.001), whereas no difference was observed between the salmeterol and the salmeterol plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				ipratropium groups. The changes in evening PEF were in favor of both active treatment arms compared with placebo (P=0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs the salmeterol group (P=0.01). The mean increase in FEV_1 was 1% predicted for placebo, 5% predicted for salmeterol, and 8% for the salmeterol plus ipratropium group (all, P=0.01). The change in FVC was 4% predicted with placebo, 7% predicted with salmeterol, and 12% predicted with salmeterol plus ipratropium. The differences between salmeterol plus ipratropium vs salmeterol alone and between salmeterol plus ipratropium vs placebo were both significant (P=0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (P=0.055). The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups. A total of 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group, and six (13%) in the salmeterol plus ipratropium group. The only significant difference was between the salmeterol plus ipratropium group and the placebo group (P=0.01).
van Noord et al.[113] (2010) Salmeterol 50 µg BID vs tiotropium 18 µg QD vs	DB, RCT, XO Patients ≥40 years of age with COPD, all current or ex-smokers with ≥10 pack-year smoking history, FEV_1 ≤60% predicted and FEV_1/FVC ≤70%	N=95 24 weeks	Primary: FEV_1, FVC, effects on dyspnea (TDI focal score), rescue albuterol use Secondary: Not reported	Primary: FEV_1 increased by 72 mL with tiotropium plus salmeterol QD compared to 97 mL with either monotherapy agent (P<0.0001). Treatment with tiotropium plus salmeterol BID provided comparable daytime bronchodilator effects (0 to 12h: 12mL; P=0.38) as tiotropium plus salmeterol QD, but significantly more bronchodilation during the night-time (12 to 24h: 73mL; P<0.0001). Clinically relevant improvements in TDI focal score were achieved with bronchodilator combinations including salmeterol QD or BID (2.56 and 2.71; P<0.005 vs monotherapy).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium 18 µg QD and salmeterol 50 µg QD vs tiotropium 18 µg QD and salmeterol 50 µg BID				Symptom benefit of combination therapies was also reflected in less need for reliever medication. All treatments were well tolerated.
Donohue et al.[114] (2002) Salmeterol 50 µg BID vs tiotropium 18 µg QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with stable COPD, FEV_1 ≤60% and FEV_1/FVC ≤70% predicted	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved by 137 mL with tiotropium compared to placebo and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL; P=0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (P=0.01). Secondary: PEFR improved by 27.3, 21.4, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (P=0.001) and tiotropium was better than salmeterol in improving evening PEFR (P=0.05). At 6 months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference 0.78 units, P=0.05). At 6 months, the mean improvement in SGRQ was -5.14 units for tiotropium (P=0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance.
Brusasco et al.[115]	DB, DD, PC, RCT	N=1,207	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Salmeterol 50 µg BID vs tiotropium 18 µg QD vs placebo	Patients with ≥40 years of age with COPD, FEV_1 ≤65% and FVC ≤70% predicted	6 months	Exacerbations, health resource use, restricted activity Secondary: Quality of life (SGRQ), dyspnea (TDI focal score), spirometry, adverse events	Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (P=0.01). There was no significant difference with salmeterol compared to placebo. The proportion of patients with at least one exacerbation was 32, 35, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (P>0.05). Fewer COPD exacerbations/patient year occurred in the tiotropium group (1.07) than in the placebo group (1.49; P<0.05). The salmeterol group did not differ from placebo (1.23 events/year). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant. The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared with 11.1 days in the salmeterol group and 10.9 days in the placebo group (P<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the six month trial for the tiotropium, salmeterol, and placebo groups, respectively. A significant difference was observed for tiotropium vs placebo (P=0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (P=0.001 and P=0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17). Tiotropium was statistically better than salmeterol in peak FEV_1 and AUC

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				from 0 to three hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%).
Briggs et al.[116] (2005) Salmeterol 50 µg BID vs tiotropium 10 µg QD	DB, PG, RCT Patients with COPD	N=653 12 weeks	Primary: Lung function Secondary: Not reported	Primary: After 12 weeks, the average post-dose FEV_1 over 12 hours was significantly higher with *tiotropium* compared with *salmeterol* (167 vs 130 mL, respectively; P=0.03). Peak FEV_1 was significantly higher with *tiotropium* compared with *salmeterol* (262 vs 216 mL, respectively; P=0.01). The average FEV_1 responses from 0 to six hours and six to 12 hours were higher in the *tiotropium* group compared with *salmeterol* (P<0.05). Peak and average FVC were significantly higher with *tiotropium* compared with *salmeterol* (P<0.01). Morning pre-dose FEV_1 responses were not significantly different among the treatment groups. T*iotropium* demonstrated a significantly higher pre-dose FVC than *salmeterol* (P<0.05). Secondary: Not reported
Rabe et al.[117] (2008) Salmeterol 50µg BID and fluticasone 500 µg BID vs	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <80% and FEV_1/FVC ≤70% predicted at visit 1,	N=605 6 weeks	Primary: FEV_1 AUC 0 to 12 h and peak FEV_1 Secondary: Peak FVC and FVC AUC 0 to 12; morning predose FEV1 and FVC	Primary: The FEV_1 $AUC_{0–12}$ mean difference was 78 mL higher in patients receiving tiotropium + formoterol compared to those receiving salmeterol + fluticasone (P=0.0006). The difference in peak FEV_1 was 103 mL in favor of tiotropium+formoterol (P=0.0001). Secondary: The 12-h FVC profile and peak FVC were significantly higher with tiotropium+formoterol compared to salmeterol+fluticasone (P=0.0001). There was no significant difference in predose FEV_1, however the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tiotropium 18 µg QD and formoterol 12 µg BID	and pre bronchodilator FEV_1 ≤65% predicted at visit 2			difference in predose FVC favored tiotropium+formoterol (P=0.05).
Ohar et al.[118] (2014) Salmeterol 50µg BID (SAL) vs fluticasone propionate-salmeterol 250-50 µg BID (FP/SAL)	AC, DB, PG, RCT Patients with COPD aged ≥40 years with recent (≤14 days) history of exacerbation requiring: hospitalization for ≤10 days, emergency room observation of duration ≥24 hours during which oral steroids ±antibiotics treatment was administered, or physician's office or emergency room visit of <24 hours duration with steroids ±antibiotics treatment plus 6-month history of exacerbation-related hospitalization	N=639 26 weeks	Primary: Estimated annualized rate of exacerbations requiring hospitalization Secondary: Rate of exacerbations requiring treatment with oral steroids, antibiotics, and/or hospitalization	Primary: There was no statistically significant treatment difference in rates of recurrent severe exacerbations (treatment ratio 0.92 [95% CI, 0.58 to 1.45]) and moderate/severe exacerbations (0.82 [0.64 to 1.06]) between FP/SAL and SAL in the intent-to-treat population. Secondary: Pre-dose morning FEV_1 change from baseline was greater (0.10 L [0.04 to 0.16]) with FP/SAL than SAL. No treatment difference was seen for other endpoints including patient-reported health outcomes and biomarker levels for the full cohort.
Beeh et al.[119] (2016) ENERGITO Salmeterol-fluticasone propionate (50-500	AC, DB, MC, RCT, XO Patients ≥40 years of age with COPD, smoking history >10 pack-years,	N=229 6 weeks	Primary: Change in FEV_1 AUC_{0-12} Secondary: Change in FEV_1 AUC_{0-24}, trough	Primary: FEV_1 $AUC_{0–12}$ (primary end point), FEV_1 $AUC_{0–24}$, and FEV1 $AUC_{12–24}$ after six weeks of treatment were increased from baseline by >120 mL in all treatment arms, with greater increases at both dose levels of once-daily tiotropium-olodaterol compared to twice-daily salmeterol-fluticasone propionate. Treatment comparisons for the primary end point revealed improvements in FEV_1 $AUC_{0–12}$ with either dose of tiotropium-olodaterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg and 50-250 µg) via Accuhaler® BID vs tiotropium-olodaterol (5-5 µg and 2.5-5 µg) via Respimat® QD	post-bronchodilator FEV_1 <70% and FEV_1/FVC ≤70% predicted		FEV_1 response, adverse events	compared to either dose of salmeterol-fluticasone, ranging from 103 mL to 129 mL (P<0.0001 for all comparisons). Secondary: Analysis of the key secondary end point of FEV_1 $AUC_{0–24}$ response showed greater improvements with either dose of tiotropium-olodaterol versus either dose of salmeterol-fluticasone propionate, ranging from 65 mL to 86 mL (P<0.0001 for all comparisons). Tiotropium-olodaterol gave greater improvements in trough FEV_1 after six weeks of treatment compared to both doses of salmeterol-fluticasone propionate, with improvements of 58 mL and 54 mL with tiotropium-olodaterol 5/5 µg and 2.5/5 µg, respectively, versus salmeterol-fluticasone propionate 50/500 µg (P<0.001 for all comparisons).
Calverley et al.[120] (2018) DYNAGITO Tiotropium 5 µg once daily vs tiotropium-olodaterol 5 µg-5 µg once daily	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history of ≥10 pack-years, FEV_1 ≤60% predicted, FEV_1/FVC <70%, and ≥1 moderate or severe exacerbation in the preceding year	N=7,880 52 weeks	Primary: Rate of moderate and severe COPD exacerbations from the first dose of medication until one day after last drug administration Secondary: Time to first moderate or severe COPD exacerbation during the treatment period, rate of exacerbations leading to hospitalization, time to first exacerbation leading to	Primary: The rate ratio for the rate of moderate and severe exacerbations was 0.93 (99% CI, 0.85 to 1.02) with tiotropium–olodaterol compared with tiotropium during the 52-week treatment period. The targeted significance level of 0.01 (i.e., necessitating a P<0.01) was not met, with a P-value of 0.0498. Secondary: The HR for time to first moderate or severe COPD exacerbation was 0.95 (99% CI, 0.87 to 1.03; P=0.12) with tiotropium–olodaterol versus tiotropium during the 52-week treatment period; the HR for time to first COPD exacerbation leading to hospitalization was 0.93 (95% CI, 0.82 to 1.06; P=0.28). For severe exacerbations, the rate ratio for tiotropium–olodaterol compared with tiotropium was 0.89 (95% CI, 0.78 to 1.02; P=0.090), and for exacerbations leading to hospitalization the rate ratio was 0.89 (95% CI, 0.76 to 1.03; P=0.13). Time to all-cause mortality was similar with tiotropium–olodaterol compared with tiotropium (HR, 0.88; 95% CI, 0.68 to 1.15).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalization, and time to all-cause mortality	
Donohue et al.[121] (2013) Umeclidinium-vilanterol (UMEC/VI) 62.5-25 µg vs UMEC 62.5 µg monotherapy vs VI 25 µg monotherapy vs placebo	DB, PC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <70% and FEV_1/FVC ≤70% predicted, score ≥2 on the modified Medical Research Council Dyspnea Scale	N=1532 24 weeks	Primary: Pre-dose trough FEV_1 on treatment Day 169 Secondary: Additional FEV_1 and FVC parameters at specified time points, quality of life	Primary: Statistically significant improvements in trough FEV_1 at Day 169 were observed for UMEC/VI 62.5-25 µg, UMEC 62.5 µg, and VI 25 µg compared with placebo (all P<0.001). Increases with UMEC/VI were significantly greater than monotherapies (P≤0.004). Secondary: Greater increases from baseline in 0–6 hour weighted mean FEV_1 were observed with UMEC/VI 62.5-25 µg, UMEC 62.5 µg, and VI 25 µg compared with placebo (0.242 L, 0.150 L and 0.122 L; all P<0.001). Similarly, greater increases were observed for UMEC/VI 62.5-25 µg compared with UMEC 62.5 µg (0.092 L; P<0.001) and VI 25 µg (0.120 L; P<0.001). All active treatment groups increased TDI focal score at Day 168 and throughout the study compared with placebo. Over the 24-week study period, all active treatments resulted in less rescue salbutamol use compared with placebo. On-treatment COPD exacerbations were reported in 13% of patients in the placebo group and 7 to 9% in active treatment groups. The incidence of treatment-emergent adverse events was similar across treatment groups.
Donohue et al.[122] (2014) Umeclidinium 125 µg vs umeclidinium-vilanterol 125-25 µg vs	DB, MC, PC, PG, RCT Current or former smokers of ≥40 years of age, with a smoking history of ≥10 pack-years and an established clinical history of COPD	N=562 52 weeks	Primary: Safety, trough FEV_1, trough FVC Secondary: Not reported	Primary: The incidence of on-treatment adverse events (AEs), serious AEs (SAEs) and drug-related AEs was similar across active treatment groups and placebo. Greater mean changes from baseline in trough FEV_1 and FVC were demonstrated for umeclidinium-vilanterol and umeclidinium compared with placebo at all visits. At 12 months, umeclidinium-vilanterol and umeclidinium had improved trough FEV_1 in comparison with placebo by 0.231 L (95% CI, 0.153 to 0.310) and 0.178 L (95% CI, 0.098 to 0.258), respectively, and trough FVC by 0.252 L (95% CI, 0.135 to 0.368) and 0.194 L (95% CI, 0.076 to 0.312), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				There were fewer patients reporting COPD exacerbations with umeclidinium-vilanterol and umeclidinium (13 and 15%) compared with placebo (24%). Secondary: Not reported
Siler et al.[123] (2016) Umeclidinium and vilanterol 62.5/25 µg inhaled daily (UMEC/VI) vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, post-bronchodilator FEV_1 <70%, score ≥2 on the modified Medical Research Council Dyspnea Scale	N=496 12 weeks	Primary: SGRQ Secondary: Rescue albuterol use, trough FEV_1 on day 84	Primary: Change from baseline in SGRQ total score had improved at day 84 with UMEC/VI versus placebo (−4.03; 95% CI, −6.28 to −1.79; P<0.001). The improvement was deemed clinically meaningful as it exceeded the minimum clinically important difference of four units. Secondary: Change from baseline in trough FEV_1 had statistically significantly improved at day 84 with UMEC/VI versus placebo (122 mL; 95% CI, 71 to 172; P<0.001). Rescue albuterol use at baseline was similar in the UMEC/VI (3.4 puffs/day) and placebo (3.8 puffs/day) groups. The mean change from baseline in rescue albuterol use over weeks one to 12 was −1.4 puffs/day and −0.6 puffs/day with UMEC/VI and placebo, respectively. UMEC/VI resulted in a reduction in rescue albuterol use versus placebo (−0.7 puffs/day; 95% CI, −1.1 to −0.4; P<0.001).
Donohue et al.[124] (2015) Umeclidinium and vilanterol 62.5/25 µg inhaled daily vs fluticasone propionate and salmeterol 250/50 µg inhaled BID	DB, DD, PG, MC, RCT Patients ≥40 years of age with a diagnosis of moderate to severe COPD, post-albuterol FEV_1 30 to 70% of predicted, pre and post albuterol FEV_1 to FVC ratio <0.70, and ≥10 pack-year	Study 1: N= 706 12 weeks Study 2: N= 697 12 weeks	Primary: 24 hour weighted mean FEV_1 on day 84 Secondary: Trough FEV_1 on day 85 and safety outcomes	Primary: The 24 hour weighted mean FEV_1 improved from baseline in both groups. The LS mean change from baseline was greater in the umeclidinium-vilanterol group than the fluticasone propionate-salmeterol group (Study 1: treatment difference 0.074 L; 95% CI, 0.038 to 0.110; P<0.001; Study 2: treatment difference 0.101 L; 95% CI, 0.063 to 0.139 P<0.001). Secondary: The trough FEV_1 improved from baseline in both groups. The LS mean change from baseline was greater in the umeclidinium-vilanterol group than the fluticasone propionate-salmeterol group (Study 1: treatment difference 0.082 L; 95% CI, 0.045 to 0.119; P<0.001; Study 2: treatment difference 0.098 L; 95% CI, 0.059 to 0.137; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(The results of two studies with the same methodology were reported in one manuscript)	smoking history without a serious exacerbation in the past year			Rates of adverse events were similar between treatment groups. Adverse events occurred in 26% of patients (Study 1) and 30% of patients (Study 2) in the umeclidinium-vilanterol group versus 27% of patients (Study 1) and 31% of patients (Study 2) in the fluticasone propionate-salmeterol group. Rates of COPD exacerbations were also similar between groups. COPD exacerbations occurred in 3% of patients in each of the umeclidinium-vilanterol and fluticasone propionate-salmeterol groups in both Study 1 and Study 2.
Singh et al.[125] (2015) Umeclidinium and vilanterol 62.5/25 µg inhaled daily vs fluticasone propionate and salmeterol 500/50 µg inhaled BID	DB, DD, PG, MC, RCT Patients ≥40 years of age with a diagnosis of COPD, post-salbutamol FEV_1 30 to 70% of predicted, pre and post albuterol FEV_1 to FVC ratio <0.70, and ≥10 pack-year smoking history	N=717 12 weeks	Primary: 24 hour weighted mean FEV_1 on day 84 Secondary: Trough FEV_1 on day 85 and safety outcomes	Primary: On Day 84, umeclidinium-vilanterol caused a significantly greater improvement of 0.080 L (95% CI, 0.046 to 0.113; P<0.001) in the least squares mean change from baseline in the primary endpoint versus fluticasone propionate-salmeterol. Secondary: Umeclidinium-vilanterol statistically significantly improved the least squares mean change from baseline in trough FEV_1 on Day 85 by 0.090 L (95% CI, 0.055 to 0.125; P<0.001) versus fluticasone propionate-salmeterol. Both treatments demonstrated a clinically meaningful improvement in symptoms (Transition Dyspnea Index ≥1 unit) and quality of life (SGRQ total score ≥4 unit decrease from baseline) over 12 weeks. The incidence of adverse events was 28% (umeclidinium-vilanterol) and 29% (fluticasone propionate-salmeterol); nasopharyngitis and headache were most common.
Feldman et al.[126] (2017) Umeclidinium/ vilanterol 62.5/25 µg once daily (UMEC/VI) vs tiotropium/ olodaterol 5/5 µg once daily	OL, RCT, XO Patients ≥40 years of age with a clinical history of COPD, post-bronchodilator FEV_1 ≤70% of predicted and 50% or more of predicted normal values who were not receiving inhaled	N=236 Each treatment group for 8 weeks with an interim 3-week washout	Primary: Change from baseline in trough FEV_1 at week 8 in the per-protocol population Secondary: Additional spirometry parameters, safety	Primary: The change from baseline in trough FEV_1 at week eight was greater in the UMEC/VI group than the TIO/OLO group (difference, 53 mL; 95% CI, 26 to 80 mL; P<0.001) in the per-protocol population. Secondary: A greater number of patients achieved a clinically meaningful increase in trough FEV_1 (100 mL or more from baseline) with UMEC/VI compared with TIO/OLO at both week four and week eight (ITT population). Overall, 52% of individuals achieved a clinically meaningful increase (100 mL or more) in trough FEV_1 from baseline with UMEC/VI compared with TIO/OLO, 29% of individuals showed similar clinical benefits for both treatments (less than 100-mL difference), and 19% achieved a clinically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(TIO/OLO)	corticosteroid therapy			meaningful increase (100 mL or more) with TIO/OLO compared with UMEC/VI. The adverse event profile was similar between treatment groups (25% vs 31% for UMEC/VI vs TIO/OLO). The most frequently reported adverse events were upper respiratory tract infections (viral or nonviral), cough, and diarrhea. The incidence of COPD exacerbations was low and similar between treatment groups.
Lipson et al.[127] (2018) IMPACT Fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg (triple therapy) once daily vs fluticasone furoate-vilanterol 100-25 µg once daily vs umeclidinium-vilanterol 62.5-25 µg once daily	DB, MC, PG, RCT Patients ≥40 years of age with symptomatic COPD, post-bronchodilator FEV_1 ≤50% of predicted and a history of at least one moderate or severe exacerbation in the previous year, or an FEV_1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year	N=10,355 52 weeks	Primary: Annual rate of moderate or severe COPD exacerbations Secondary: Trough FEV_1, SGRQ score	Primary: The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% CI, 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). Secondary: For the spirometric outcome of the mean change from baseline in trough FEV_1, the difference between the triple-therapy and fluticasone furoate–vilanterol groups was 97 ml (95% CI, 85 to 109; P<0.001), and the difference between the triple-therapy and umeclidinium–vilanterol groups was 54 ml (95% CI, 39 to 69; P<0.001). There were significant differences between the triple-therapy group and the fluticasone furoate–vilanterol and umeclidinium–vilanterol groups in the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least four points (P<0.001 for both comparisons on both outcomes).
Exercise-Induced Bronchospasm				
Berkowitz et al.[128] (1986) Albuterol MDI 0.18 mg 15	RCT, SB, XO Patients 12 to 17 years of age with asthma and	N=18 4 days	Primary: Mean percent increase in FEV_1 five minutes after medication, mean	Primary: The mean increase in percentage of predicted FEV_1 was significantly higher five minutes post administration of albuterol or metaproterenol than with placebo (P<0.0005). A significantly greater increase was also seen five minutes after the administration of metaproterenol when compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
minutes prior to exercise vs metaproterenol MDI 1.3 mg 15 minutes prior to exercise vs placebo	exercised-induced bronchospasm (FEV_1 >20% of pre-exercise level) following a treadmill exercise test		workload for exercise challenges, mean decrease in FEV_1 from baseline, and the number of patients in whom broncho-constriction was blocked over time Secondary: Not reported	with albuterol (P<0.01). On the days when the subjects received the active medications, the mean workloads were not found to be significantly different. Following the initial post-medication exercise test, a majority of patients in the placebo group experienced exercise-induced spasm compared to both active ingredient groups. This was a significant difference (P<0.0005) between the placebo and active ingredient groups, but not between the active ingredient groups themselves. Following the two-hour exercise challenge, the remainder of the placebo group experienced exercise-induced spasm and a greater number in the remaining metaproterenol group compared to the albuterol group experienced exercise-induced spasm. There was a greater decrease in mean maximum decrease in FEV_1 in the placebo group compared to the active ingredient groups, which was found to be statistically significant (P<0.001). Albuterol prevented exercise-induced bronchospasm in more patients and for a significantly longer time than metaproterenol did (P<0.05).
Shapiro et al.[129] (2002) Albuterol 180 µg prior to exercise challenge vs formoterol 12 µg prior to exercise challenge vs formoterol 24 µg prior to exercise	DD, XO Patients 12 to 50 years of age with a baseline FEV_1 >70% and ≥20% reduction in FEV_1 after 2 exercise challenges, 4 hours apart	N=20 4 test sequences	Primary: Maximum percent decrease in FEV_1 after each exercise challenge Secondary: Length of coverage, rescue therapy, and tolerability	Primary: Both formoterol doses produced significantly greater inhibition of FEV_1 decrease compared to placebo at all points in time (P<0.01). In addition, both formoterol doses produced significantly greater inhibition of FEV_1 compared to albuterol at all points in time, with the exception of 15 minutes post dose (P<0.01). The two formoterol dose groups were not statistically different from each other. The only point in time that the mean maximum percent decrease in $FEV_1$with albuterol was statistically different from placebo was 15 minutes post dose (P<0.05). Secondary: For length of coverage, 89 to 94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Seventy-one percent of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
challenge vs placebo				albuterol and 29% receiving placebo. Nineteen percent of patients treated with albuterol required a rescue inhaler at least once compared to 0% of patients receiving formoterol. There was no statistical difference in the percent of patients experiencing adverse effects in all of the groups.
Pearlman et al.[130] (2006) Formoterol 12 to 24 µg vs albuterol 180 µg vs placebo	DB, RCT, XO Patients 4 to 11 years of age with exercise-induced bronchoconstriction	N=23 4 treatment periods	Primary: Maximum percent decrease in FEV_1 from the pre-exercise value after exercise challenge tests (six minute treadmill) conducted 15 minutes and four, eight, and 12 hours after give the dose Secondary: Not reported	Primary: The maximum percentage decrease in FEV_1 after the four hour exercise test was significantly less for formoterol, 12 and 24 µg, vs placebo ($P<0.001$ for both) or albuterol ($P=0.016$ and $P=0.010$, respectively). Albuterol was not significantly different from placebo. Formoterol, 12 and 24 µg, differed from placebo at eight hours ($P=0.002$ and $P=0.001$, respectively), with a smaller difference between albuterol and placebo ($P=0.045$). Protection against EIB (<20% maximum decrease in FEV_1) across all time points was observed for 77 and 74% of children with formoterol, 12 and 24 µg, respectively, compared with 35% with albuterol and 27% with placebo. Secondary: Not reported
Richter et al.[131] (2002) Formoterol 12 µg prior to exercise challenge vs salmeterol 50 µg prior to exercise challenge	DB, DD, PC, RCT, XO Patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), AUC of percent change in FEV_1 from end of exercise to 90 minutes	Primary: At 5 minutes, there was a significantly greater response with terbutaline than salmeterol ($P<0.001$). At 5, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol ($P<0.05$). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared with placebo at 30 and 60 minute intervals ($P<0.01$) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the five-minute interval ($P<0.05$). A significant decrease was seen in AUC with increasing time between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbutaline 500 µg prior to exercise challenge vs placebo	methacholine		Secondary: Not reported	inhalation and exercise with terbutaline, formoterol, and salmeterol (P<0.01); however, there was no difference between treatments. Secondary: Not reported
Edelman et al.[132] (2000) Salmeterol 100 µg BID vs montelukast 10 mg QD	DB, PG, RCT Patients 15 to 45 years of age with asthma, nonsmokers for ≥1 year, smoking history ≤15 pack-years, decrease in FEV_1 of ≥20% after a standardized exercise challenge	N=191 8 weeks	Primary: Change from baseline in the maximal percentage decrease in FEV_1 at the end of eight weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days one to three and week four, the time required after maximal decrease to return to within 5% of pre-challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of	Primary: By day three, similar reductions in maximal percentage decrease in FEV_1 were seen with both therapies. Sustained improvement occurred in the montelukast group at weeks four and eight; however, at these time points, the bronchoprotective effect of salmeterol decreased significantly. At week eight, the percentage inhibition in the maximal percentage decrease in FEV_1 was 57.2% in the montelukast group and 33.0% in the salmeterol group (P=0.002). By week eight, 67% of patients receiving montelukast and 46% of patients receiving salmeterol had a maximal percentage decrease in FEV_1 of <20%. Secondary: Improvement in maximal percent decrease in FEV_1 was similar in both groups between days one to three, and was maintained at week four in the montelukast group but not in the salmeterol group (P=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre-challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (P<0.001, P<0.001, P=0.010, P<0.001). Approximately 26% of patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 40% in the salmeterol group (P=0.044). After 8 weeks, 66.7% of patients in the montelukast group achieved a decrease in FEV_1 of <20% after exercise challenging compared to 45.6% of patients receiving salmeterol (P=0.028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			exercise test, and the number and percent of patients whose decrease in FEV_1 from pre-exercise levels was <10%, 10 to 20%, 20 to 40% and >40%	Both medications were generally well tolerated.
Storms et al.[133] (2004) Salmeterol 50 µg QD vs montelukast 10 mg QD vs placebo	DB, MC, PG, RCT Patients 15 to 45 years of age with asthma, documentation of exercise-induced bronchospasm, and uncontrolled on ICS for at least 2 months	N=122 4 weeks	Primary: Effect on the maximum FEV_1 Secondary: Effects of treatment on pre-exercise FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average clinic exercise-assessment questionnaire	Primary: After 4 week, the maximum post-rescue medication FEV_1 improved in the montelukast and placebo group, but not in the salmeterol group (1.5, 1.2 and -3.9%, respectively). The maximum FEV_1 was significantly less in the salmeterol group compared to the montelukast ($P<0.001$) and placebo group ($P<0.001$). The difference between the montelukast and placebo groups was not significant. Secondary: There was a significant improvement in the mean change from baseline in pre-exercise FEV_1 in the salmeterol group compared to the placebo (at week 1, $P<0.001$) and montelukast group (at weeks one and four; $P=0.010$). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased exercise-induced bronchospasm at week four compared to placebo ($P=0.008$), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after four weeks of treatment montelukast permitted significantly faster rescue with beta-adrenergic agonists ($P=0.036$, $P=0.005$). After four weeks, there was a significant difference in the clinic exercise-assessment questionnaire score immediately and 10 minutes after exercise with montelukast compared to placebo ($P<0.020$).

*Eformoterol=formoterol (formerly known as eformoterol in the UK)

Drug regimen abbreviations: QD=once daily, BID=twice daily, TID=three times daily, QID=four times daily
Study abbreviations: CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, IB=investigational blinded, MC=multicenter, Meta=meta-analysis, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blinded, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, COPD=chronic obstructive pulmonary disease, ED=emergency department, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, ICS=inhaled corticosteroid, LABA= long-acting β-agonist, LOS=length of stay, LTRA=leukotriene receptor antagonist, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, SAE=serious asthma exacerbations, SGRQ=St. George's respiratory questionnaire, TDI=transition dyspnea index score

Additional Evidence

Dose Simplification
Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[134] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[134] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[134] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[135] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[136] Bunnag et al. evaluated albuterol in the form of a dry powder inhaler, a metered dose inhaler with a chlorofluorocarbon (CFC) propellant, and a metered dose inhaler with a hydrofluoroalkane (HFA) propellant in patients with asthma and chronic obstructive pulmonary disease (COPD).[137] After receiving all three forms of albuterol, patients completed an evaluation questionnaire indicating their preferences. The dry powder inhaler was preferred by 47.5% of patients, followed by the HFA metered dose inhaler (32.5%) and the CFC metered dose inhaler (20%). There was no difference noted in the ease of use among the 3 devices in 59.9% of subjects. Barta et al. mailed a survey to 82 patients (most with COPD) using a home nebulizer treatment.[138] It consisted of 29 questions covering topics of well-being, symptom control, self-confidence, dependency, time, and technical issues, side effects, and compliance. In the questionnaire, 98% of patients reported the benefits of using a nebulizer outweighed the disadvantages. The perceived advantages were the ability to control symptoms and be less dependent on health care providers, hospitals and care givers. When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[134]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 14. Relative Cost of the Respiratory Beta-Adrenergic Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Albuterol	aerosol inhaler*, dry powder inhaler, extended-release tablet*, inhalation solution*, syrup*, tablet*	ProAir Digihaler®, ProAir HFA®*, Proventil HFA®*, ProAir Respiclick®, Ventolin HFA®*	$$$	$$
Arformoterol	inhalation solution	Brovana®	$$$$$	N/A
Formoterol	inhalation solution, dry powder inhaler	Foradil®, Perforomist®	$$$$$	N/A
Levalbuterol	aerosol inhaler, inhalation solution	Xopenex®*, Xopenex HFA®*	$$$	$$
Metaproterenol	syrup*, tablet*	N/A	N/A	$$$$
Olodaterol	solution inhaler	Striverdi Respimat®	$$$$$	N/A
Salmeterol	dry powder inhaler	Serevent Diskus®	$$$$$	N/A
Terbutaline	injection*, tablet*	N/A	N/A	$$$$$
Combination Products				
Aclidinium and formoterol	aerosol inhaler	Duaklir Pressair®	$$$$$	N/A
Glycopyrrolate and formoterol	aerosol inhaler	Bevespi®	$$$$$	N/A
Ipratropium and albuterol	inhalation solution, solution inhaler	Combivent Respimat®	$$$$$	$
Tiotropium and olodaterol	solution inhaler	Stiolto Respimat®	$$$$$	N/A
Umeclidinium and vilanterol	dry powder inhaler	Anoro Ellipta®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The respiratory beta-adrenergic agonists (β_2-agonists) are approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and exercise-induced bronchospasm.[1-19] They are often classified as short- or long-acting agents based on differences in their pharmacokinetic properties. In 2019 a new combination product containing aclidinium and formoterol was approved for the maintenance treatment of patients with COPD.[13] Combination products are available with aclidinium, glycopyrrolate, ipratropium, tiotropium, and umeclidinium, which are all anticholinergic agents.[1,2] The respiratory β_2-agonists are available in a variety of dosage forms, including aerosol inhaler, dry powder inhaler, immediate-release tablets, inhalation solution, sustained-release tablets, and syrup. Albuterol (aerosol inhaler, immediate-release tablets, inhalation solution, sustained-release tablets, and syrup), ipratropium-albuterol (inhalation solution), levalbuterol (inhalation solution and aerosol inhaler), metaproterenol (syrup) and terbutaline (injection and tablets) are available in a generic formulation.

The 2021 Global Initiative for Asthma (GINA) includes recommendations published in 2019, prompted by concerns about the risks and consequences of the long-standing approach of initiating asthma treatment with short-acting β_2-agonists (SABA) alone. "For safety, GINA no longer recommends treatment of asthma in adolescents and adults with SABA alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment."[23] For the controller management of asthma, low-dose ICS is recommended.[23] When additional therapy is needed, guidelines recommend the use of a medium dose ICS and then adding on long-acting antimuscarinic agent (LAMA) for adults and adolescents over 12 years of age. For children six to 11 years of age, guidelines recommend use of ICS-long-acting β_2-agonist (LABA) combination when additional therapy is needed The use of an oral LABA is not recommended due to potential adverse events.[23] LABAs should not be used as

monotherapy since they do not affect airway inflammation. Guidelines do not give preference to one short- or long-acting β_2-agonist over another for the treatment of asthma.

In May 2019 the boxed warnings were removed from arformoterol, formoterol, olodaterol, glycopyrrolate-formoterol, tiotropium-olodaterol, and umeclidinium-vilanterol, and warnings were added for serious asthma-related events. The warning states that use of LABAs as monotherapy [without ICS] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.[1-19]

For the treatment of asthma, several comparative studies have demonstrated similar improvements in respiratory endpoints with the use of short-acting β_2-agonists; however, a few studies have demonstrated greater efficacy with one agent over another. The LABAs have been shown to be more effective than the routine use of short-acting β_2-agonists for the maintenance treatment of asthma. Clinical studies directly comparing the LABAs have also demonstrated similar outcomes for the majority of the endpoints assessed, including their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on inhaled corticosteroids alone. There does not appear to be a difference in adverse events with the LABAs.[139-141]

For the treatment of COPD, most studies have indicated that respiratory medications do not modify the long-term decline in lung function; therefore, the goal of treatment is to decrease symptoms and complications.[20-22] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline was updated in 2022. Initiation of maintenance pharmacological therapy should be based on the individualized assessment of symptoms and exacerbation risk. Generally, a long-acting β_2 agonist (LABA) or long-acting antimuscarinic agent (LAMA) is recommended when beginning treatment. Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation.[20] Treatment guidelines do not indicate a preference as there is insufficient evidence to favor one long-acting bronchodilator over another.[20-22] Regular treatment with long-acting bronchodilators are more effective than treatment with short-acting bronchodilators.[20-22] Studies directly comparing the LABAs have demonstrated similar improvements in some, but not all, respiratory endpoints. Some studies suggest that formoterol may have a faster onset of action than salmeterol. Tiotropium may provide a greater clinical benefit than LABAs with regards to spirometric endpoints, dyspnea, exacerbations, quality of life, and health care resource utilization. Combining an inhaled antimuscarinic with a β_2-agonist has also been shown to be more effective than monotherapy.

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[134] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[134] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[134]

Therefore, all brand short-acting respiratory beta-adrenergic agonists within the class reviewed are comparable to each other and to the generic products (if available) and offer no significant clinical advantage over other alternatives in general use. The brand long-acting respiratory beta-adrenergic agonists offer significant clinical advantages over the short-acting respiratory beta-adrenergic agonists and are comparable to each other and to the generic products (if available). However, for patients with asthma, the long-acting respiratory beta-adrenergic agonists are not recommended as first-line therapy. For patients with COPD, the long-acting respiratory beta-adrenergic agonists do not offer significant clinical advantages over other long-acting inhaled bronchodilators (e.g., inhaled antimuscarinics). Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

XI. Recommendation

No brand respiratory beta-adrenergic agonist is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Leukotriene Modifiers
AHFS Class 481024
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I. Overview

The leukotriene modifiers are approved for the long-term management of patients with asthma.[1-6] Montelukast is also approved for the treatment of symptoms of seasonal and perennial allergic rhinitis, as well as for the prevention of exercise-induced bronchoconstriction.[3] Cysteinyl leukotrienes play an important role in the pathophysiology of asthma and contribute to bronchoconstriction, increased airway responsiveness, mucous secretion, and the recruitment of inflammatory cells. Blocking the action of cysteinyl leukotrienes has been shown to reduce or prevent airway obstruction and decrease the activation of inflammatory cells.[7]

The leukotriene modifiers can be divided into two subtypes: leukotriene receptor antagonists and 5-lipoxygenase inhibitors. The leukotriene receptor antagonists (montelukast and zafirlukast) block the leukotriene receptor and inhibit the action of cysteinyl leukotrienes.[3,4] Zileuton is the only 5-lipoxygenase inhibitor currently available. It inhibits the actions of the 5-lipoxygenase enzyme, thereby preventing the formation of leukotrienes.[5,6] All of the leukotriene modifiers elicit a similar biologic response, but differ in their dosing requirements, adverse events, drug interactions, and pharmacokinetic parameters.[1-6]

The leukotriene modifiers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Leukotriene Modifiers Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Montelukast	chewable tablet, granules, tablet	Singulair®*	montelukast
Zafirlukast	tablet	Accolate®*	zafirlukast
Zileuton	sustained-release tablet*, tablet	Zyflo®	none

*Generic available in at least one dosage form and/or strength.
‡Generic product requires prior authorization.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the leukotriene modifiers are summarized in Table 2.

Table 2. Treatment Guidelines Using the Leukotriene Modifiers

Clinical Guideline	Recommendation(s)
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2021)**[8]	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences. • For population-level decisions about asthma treatment, the 'preferred option'

Clinical Guideline	Recommendation(s)
	represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk. • For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues. <u>Medications and strategies for symptom control and risk reduction</u> • For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone. • This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms. • Choice of reliever o Low dose ICS-formoterol is the preferred approach recommended by this guideline. o SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy. • Mild asthma o Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death. o In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. • Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique o Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities. ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium. ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age. ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA. ▪ For children, try other controller options at the same step before stepping up. ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. • Stepping down to find the minimum effective dose o Consider step down once good asthma control has been achieved and maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. • For all patients with asthma

Clinical Guideline	Recommendation(s)
	○ Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect. ○ Encourage adherence with controller medication, even when symptoms are infrequent. ○ Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations. ○ For patients with one or more risk factors for exacerbations: ▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function). ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies). • Difficult-to-treat and severe asthma ○ Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics. <u>Categories of asthma medications</u> • *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise. • *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment. • *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. <u>Initial controller treatment</u> • For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made. <u>Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u> • Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment. • If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment: ○ Incorrect inhaler technique.

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>

Poor adherence.
Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
Comorbidities that may contribute to respiratory symptoms and poor quality of life.
Incorrect diagnosis.

<table>
<tr><th colspan="6">Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)</th></tr>
<tr><td rowspan="2">Controller and preferred reliever (Track 1)</td><td colspan="2">Steps 1 to 2
As-needed low dose ICS-formoterol</td><td>Step 3
Low dose maintenance ICS-formoterol</td><td>Step 4
Medium dose maintenance ICS-formoterol</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol</td></tr>
<tr><td colspan="5">Reliever: as-needed low-dose ICS-formoterol</td></tr>
<tr><td rowspan="2">Controller and alternative reliever (Track 2)</td><td>Step 1
Take ICS whenever SABA taken</td><td>Step 2
Low dose maintenance ICS</td><td>Step 3
Low dose maintenance ICS-LABA</td><td>Step 4
Medium/high dose maintenance ICS-LABA</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA</td></tr>
<tr><td colspan="5">Reliever: as-needed SABA</td></tr>
</table>

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

<table>
<tr><th colspan="6">Personalized management to control symptoms and minimize future risk (six to 11 years of age)</th></tr>
<tr><th></th><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td>Preferred controller</td><td>Low dose ICS taken when SABA is taken</td><td>Daily low dose ICS</td><td>Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy</td><td>Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy Refer for expert advice</td><td>Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)</td></tr>
<tr><td>Other controller options</td><td>Consider daily low dose ICS</td><td>Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken</td><td>Low dose ICS+LTRA</td><td>Add tiotropium, or add LTRA</td><td>Add-on anti-IL5, or add-on low dose OCS, but consider side effects</td></tr>
<tr><td>Reliever</td><td colspan="5">As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)</td></tr>
</table>

<u>Management of worsening asthma and exacerbations</u>

Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.

</td></tr>
</table>

Clinical Guideline	Recommendation(s)
	○ The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment. ○ Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately. ○ The action plan can be based on changes in symptoms or (in adults) peak expiratory flow. • For patients presenting with an exacerbation to a primary care or acute care facility: ○ Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. ○ Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given. ○ Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be reviewed after one hour. ○ Ipratropium bromide treatment is recommended only for severe exacerbations. ○ Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment. ○ Chest X-ray or prescribing antibiotics is not routinely recommended. ○ Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. ○ Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use. • Arrange early follow-up after any exacerbation, regardless of where it was managed. ○ Review the patient's symptom control and risk factors for further exacerbations. ○ Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks. ○ Provide a written asthma action plan and advice about avoiding exacerbation triggers. ○ Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> • The goals of asthma management in young children are similar to those in older patients: ○ To achieve good control of symptoms and maintain normal activity levels. ○ To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects. • Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective. • A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are

Clinical Guideline	Recommendation(s)

uncontrolled and/or wheezing episodes are frequent or severe.

- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Personalized management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

<u>Management of worsening asthma and exacerbations in children five and younger</u>

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - There is no compelling evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%).
  - Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  - Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days for children attending an emergency department or admitted to hospital, up

Clinical Guideline	Recommendation(s)
	to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma management.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2019)[9]**	<u>Pharmacological management</u> • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%. • Intermittent reliever therapy: o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. o For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. o Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years of age with asthma. o ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: o In adults, the first choice add-on therapy to an ICS is a LABA, which should be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence.

Clinical Guideline	Recommendation(s)
	○ In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: ○ If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: ○ All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. ○ If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed) ▪ Add tiotropium (adults) ▪ Add a theophylline. ○ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). ○ Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored. ○ Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. ○ Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. ○ The use of immunotherapy is not recommended for the treatment of asthma in adults or children.
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)[10]**	<u>Pharmacologic treatment of allergic rhinitis</u> • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis.

Clinical Guideline	Recommendation(s)
	• Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma & Immunology: **Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision (2016)[11]**	<u>Should a combination of an oral H_1-antihistamine and intranasal corticosteroid vs intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an oral H_1-antihistamine or an intranasal corticosteroid alone is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H_1-antihistamine is suggested (very low certainty of evidence). • This recommendation concerns regular use of newer and less sedative oral H_1-antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis. For older oral H_1-antihistamines with more sedative effects, the balance of desirable and undesirable effects may be different. • Currently available evidence suggests that there is no additional benefit from a combination therapy compared with intranasal corticosteroid alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (very low certainty of evidence). • At initiation of treatment (approximately the first two weeks), a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine might act faster

Clinical Guideline	Recommendation(s)
	than an intranasal corticosteroid alone and thus might be preferred by some patients. The choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal H_1-antihistamine alone be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine rather than an intranasal H_1-antihistamine alone is suggested (low certainty of evidence). Should a leukotriene receptor antagonist vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either a leukotriene receptor antagonist or an oral H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an oral H_1-antihistamine rather than a leukotriene receptor antagonist is suggested (low certainty of evidence). • The choice of a leukotriene receptor antagonist or oral H_1-antihistamine will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an oral H_1-antihistamine might still be more cost-effective, but this will largely depend on availability of generic leukotriene receptor antagonists and the local cost of various newer-generation oral H_1-antihistamines and leukotriene receptor antagonists. • Some patients with allergic rhinitis who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from a leukotriene receptor antagonist more than from an oral H_1-antihistamine. However, this recommendation applies to treatment of allergic rhinitis but not to treatment of asthma. Patients with asthma who have concomitant allergic rhinitis should receive an appropriate treatment according to the guidelines for the treatment of asthma. Should an intranasal H_1-antihistamine vs an intranasal corticosteroid be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (low certainty of evidence). Should an intranasal H_1-antihistamine vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (very low certainty of evidence). • The panel members acknowledged that the choice of treatment will depend mostly on patient preferences and local availability and cost of treatment.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of**	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Oral antihistamines • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of

Clinical Guideline	Recommendation(s)
Rhinitis: An Updated Practice Parameter (2008)[12]	first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <u>Intranasal antihistamines</u> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established.

Clinical Guideline	Recommendation(s)
	• Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. <u>Intranasal anticholinergics</u> • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events.

Clinical Guideline	Recommendation(s)
	Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Treatment of seasonal allergic rhinitis, an evidence-based focused 2017 guideline update (2017)**[13]	For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age: • Routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine. • An intranasal corticosteroid is recommended over a leukotriene receptor antagonist (for ≥15 years of age). • For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.
American Academy of Allergy, Asthma & Immunology: **Rhinitis 2020: A practice parameter update (2020)**[14]	• Prescribing first-generation antihistamines is not recommended; a second-generation antihistamine is preferred when prescribing an oral antihistamine for the treatment of AR. • Clinician should not select the oral LTRA montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies. • Clinicians should not select an oral LTRA for the treatment of NAR. • For the treatment of very severe or intractable AR, the clinician may consider a short course (5 to 7 days) of oral corticosteroids. • For the treatment of very severe or intractable AR, the clinician should not prescribe a depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects. • The clinician should offer intranasal antihistamine as an initial treatment option for patients with SAR. • The clinician should offer intranasal antihistamine as a first-line monotherapy option for patients with NAR. • The clinician should offer intranasal antihistamine as a first-line option for patients with intermittent AR. • When choosing monotherapy for persistent AR, intranasal corticosteroid should be the preferred medication.

Clinical Guideline	Recommendation(s)
	• For the initial treatment of moderate/severe SAR in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over an LTRA. • The use of intranasal decongestants should be short term and be used for intermittent or episodic therapy of nasal congestion. • In patients having severe mucosal edema, which impairs the delivery of other intranasal agents, an intranasal decongestant should be considered for up to five days of use. • Oral decongestant agents should be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome. • Oral decongestants should be avoided during the first trimester of pregnancy. • Patients with PAR and NAR who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium. • Intranasal cromolyn should be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures. • Clinicians should consider the combination of an intranasal corticosteroid and an internasal antihistamine for the initial treatment of moderate/severe nasal symptoms of SAR in patients age ≥12 years. • Clinicians should consider the combination of an intranasal corticosteroid and an intranasal antihistamine for moderate/severe SAR, PAR and NAR that is resistant to pharmacologic monotherapy. • For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium. • Patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to four weeks. • For patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician should consider the addition of pseudoephedrine, when tolerated. • For SAR, the clinician should not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine. • The clinician should not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients ≥12 years of age with symptoms of SAR. • Clinicians should not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR. • The addition of the oral LTRA montelukast to an intranasal corticosteroid for AR is not recommended. • Clinicians should offer an intranasal corticosteroid as a first-line therapy for NAR. • Clinicians should offer an intranasal antihistamine as a first-line therapy for NAR. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be offered through shared decision making to patients with moderate/severe AR who are not controlled with allergen avoidance and/or pharmacotherapy or choose immunotherapy as the preferred method of treatment and/or desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be considered for patients with controlled mild and moderate asthma with coexisting AR.

Clinical Guideline	Recommendation(s)
American Academy of Otolaryngology - Head and Neck Surgery Foundation: **Clinical Practice Guideline Allergic Rhinitis (2015)**[15]	• The clinical diagnosis of allergic rhinitis (AR) should be made when patients present with a history and physical exam consistent with an allergic cause and one or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. • Patients with a clinical diagnosis or AR who do not respond to empiric treatment, or in whom the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy, should have specific IgE (skin or blood) allergy testing. • Sinonasal imaging should not routinely be performed in patients presenting with symptoms consistent with a diagnosis or AR. • AR patients who have identified allergens that correlate with clinical symptoms may avoid known allergens or utilize environmental controls. • Patients with AR should be assessed for the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. • Intranasal steroids are recommended for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. • Oral second-generation/less-sedating antihistamines are recommended for patients with AR and primary complaints of sneezing and itching. • Intranasal antihistamines may be used in patients with seasonal, perennial, or episodic AR. • Oral leukotriene receptor antagonists should not be offered as primary therapy for patients with AR. • Combination pharmacologic therapy may be used in patients with AR who have inadequate response to pharmacologic monotherapy. • Immunotherapy (sublingual or subcutaneous) should be offered to patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the leukotriene modifiers are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Leukotriene Modifiers[1-6]

Generic Name(s)	Montelukast	Zafirlukast	Zileuton
Allergic Rhinitis			
Relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older	✔		
Asthma			
Prophylaxis and chronic treatment of asthma in patients 12 months of age and older	✔		
Prophylaxis and chronic treatment of asthma in adults and children 5 years of age and older		✔	
Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older			✔
Exercise-Induced Bronchoconstriction			

Acute prevention of exercise-induced bronchoconstriction in patients 6 years of age and older	✔		

IV. Pharmacokinetics

The pharmacokinetic parameters of the leukotriene modifiers are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Leukotriene Modifiers[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Montelukast	60 to 78	>99	Liver, extensive (% not reported)	Feces (86)	2.7 to 5.0
Zafirlukast	Not reported	99	Liver, extensive (% not reported)	Renal (10) Feces (90)	13.3
Zileuton	Not reported	93	Liver (% not reported)	Renal (95)	2.5*/3.2†

*IR=immediate-release.
†SR=sustained-release.

V. Drug Interactions

Major drug interactions with the leukotriene modifiers are listed in Table 5.

Table 5. Major Drug Interactions with the Leukotriene Modifiers[2]

Generic Name(s)	Interaction	Mechanism
Zileuton	Theophyllines	Zileuton may decrease the metabolism of theophylline compounds, and thereby increase theophylline levels.
Zileuton	Amiodarone	Concurrent use of amiodarone and zileuton may result in increased amiodarone and zileuton exposure.
Zileuton	Astemizole	Concurrent use of astemizole and zileuton may result in cardiotoxicity (QT interval prolongation, torsades de pointes, cardiac arrest).
Zileuton	Pimozide	Zileuton may inhibit the metabolism of pimozide (possibly via cytochrome P450 3A4 enzyme), potentially causing fatal cardiac arrhythmias.
Zileuton	Tizanidine	Concurrent use of tizanidine and zileuton may result in increased tizanidine plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the leukotriene modifiers are listed in Table 6. Treatment with zileuton has been associated with elevations in liver transaminases and hepatitis. Long term post-marketing surveillance studies have shown elevations in liver function tests ≥3 times the upper limit of normal, which occurred more frequently in zileuton-treated patients than in patients taking other routine asthma medications.[5,6] Cases of life-threatening hepatic failure have been reported in patients treated with zafirlukast. In most cases, symptoms resolved and liver enzymes returned to normal after discontinuation of therapy.[4] Use of montelukast has also been associated with rare post-marketing reports of liver injury and cholestatic hepatitis. In general, montelukast has been associated with fewer reports of liver injury and risk compared to zafirlukast and zileuton.[3-6]

Table 6. Adverse Drug Events (%) Reported with the Leukotriene Modifiers[1-6]

Adverse Events	Montelukast	Zafirlukast	Zileuton
Cardiovascular			
Chest pain	-	-	>1

Adverse Events	Montelukast	Zafirlukast	Zileuton
Edema	✔	✔	-
Palpitations	✔	-	-
Central Nervous System			
Agitation	✔	-	-
Aggressive behavior	✔	-	-
Dizziness	2	1.6	>1
Depression	✔	✔	-
Disorientation	✔	-	-
Dream abnormalities	✔	-	-
Drowsiness	✔	-	-
Hallucinations	✔	-	-
Headache	18	12.9	24.6
Irritability	✔	-	-
Insomnia	✔	✔	>1
Nervousness/anxiousness	✔	-	>1
Paraesthesia	✔	-	-
Restlessness	✔	-	-
Seizures	✔	-	-
Somnolence	-	-	>1
Suicidal ideation	✔	-	-
Dermatological			
Atopic dermatitis	≥2	-	-
Dermatitis	≥2	-	-
Eczema	≥2	-	-
Erythema nodosum	✔	-	-
Pruritus	✔	✔	>1
Rash	≥2	✔	✔
Rash with blistering	-	✔	-
Skin infection	≥2	-	-
Urticaria	≥2	✔	✔
Varicella	≥2	-	-
Gastrointestinal			
Abdominal pain	2.9	1.8	4.6
Constipation	-	-	>1
Diarrhea	≥2	2.8	-
Dyspepsia	2.1	1.3	8.2
Flatulence	-	-	>1
Gastroenteritis	≥2	-	-
Nausea	≥2	3.1	5.5
Pancreatitis	✔	-	-
Vomiting	✔	1.5	>1
Genitourinary			
Pyuria	1	-	-
Urinary tract infection	-	-	>1
Vaginitis	-	-	>1
Hematologic			
Agranulocytosis	-	✔	-
Bleeding abnormalities	✔	✔	-
Eosinophilia	✔	✔	-
Leukopenia	-	-	1
Hepatic			
Alanine transaminase elevations	2.1	1.5	1.9
Aspartate aminotransferase elevations	1.6	-	-
Cholestatic hepatitis	✔	-	-

Adverse Events	Montelukast	Zafirlukast	Zileuton
Hepatic eosinophilic infiltration	✔	-	-
Hepatic failure	-	✔	-
Hepatitis	-	✔	✔
Hyperbilirubinemia	-	✔	✔
Transaminase elevations	-	✔	✔
Musculoskeletal			
Arthralgia	✔	✔	>1
Back pain	-	1.5	-
Muscle cramps	✔	✔	-
Myalgia	✔	1.6	3.2
Neck pain	-	-	>1
Tremor	✔	-	-
Respiratory			
Anaphylaxis	✔	✔	-
Bronchitis	≥2	-	-
Cough	2.7	-	-
Influenza	4.2	-	-
Laryngitis	≥2	-	-
Nasal congestion	1.6	-	-
Pharyngitis	≥2	-	-
Pneumonia	≥2	-	-
Rhinitis	≥2	-	-
Rhinorrhea	≥2	-	-
Sinusitis	≥2	-	-
Upper respiratory infection	≥2	-	-
Wheezing	≥2	-	-
Other			
Accidental injury	-	1.6	3.4
Angioedema	✔	✔	-
Asthenia	1.8	1.8	3.8
Bruising	✔	✔	-
Conjunctivitis	≥2	-	>1
Ear pain	≥2	-	-
Eosinophilic pneumonia	-	✔	-
Epistaxis	✔	-	-
Fatigue	1.8	-	-
Fever	≥2	1.6	>1
Hypertonia	-	-	>1
Hypoesthesia	✔	-	-
Infection	-	3.5	-
Lymphadenopathy	-	-	>1
Malaise	-	✔	>1
Myopia	≥2	-	-
Otitis media	≥2	-	-
Pain	1.7	1.9	7.8
Tonsillitis	≥2	-	-
Tooth infection	≥2	-	-
Trauma	1	-	-
Vasculitis	✔	✔	-

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Montelukast[3]

WARNING
WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS Serious neuropsychiatric (NP) events have been reported with the use of montelukast. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The mechanisms underlying NP events associated with montelukast use are currently not well understood. Because of the risk of NP events, the benefits of montelukast may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of montelukast for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies. In patients with asthma or exercise-induced bronchoconstriction, consider the benefits and risks before prescribing montelukast. Discuss the benefits and risks of montelukast with patients and caregivers when prescribing montelukast. Advise patients and/or caregivers to be alert for changes in behavior or new NP symptoms when taking montelukast. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue montelukast and contact a healthcare provider immediately.

VII. Dosing and Administration

The usual dosing regimens for the leukotriene modifiers are listed in Table 8.

Table 8. Usual Dosing Regimens for the Leukotriene Modifiers[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Montelukast	Allergic rhinitis: Tablet: 10 mg daily at any time of day Asthma: Tablet: 10 mg daily in evening Exercise-induced bronchospasm: Tablet: 10 mg at least 2 hours before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose	Allergic rhinitis in patients 6 to 23 months of age: Granules: 4 mg once daily Allergic rhinitis in patients 2 to 5 years of age: Chewable tablet, granules: 4 mg once daily Allergic rhinitis in patients 6 to 14 years of age: Chewable tablet: 5 mg once daily Allergic rhinitis in patients ≥15 years of age: Tablet: 10 mg once daily Asthma in patients 12 to 23 months: Granules: 4 mg once daily in the evening Asthma in patients 2 to 5 years of age: Chewable tablet, granules: 4 mg once daily in the evening Asthma in patients 6 to 14 years of age: Chewable tablet: 5 mg once daily in the evening Asthma in patients ≥15 years of age: Tablet: 10 mg once daily in the evening	Chewable tablet: 4 mg 5 mg Granules: 4 mg Tablet: 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Exercise-induced bronchospasm in patients 6 to 14 years of age: Chewable tablet: 5 mg at least two hour before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose Exercise-induced bronchospasm in patients ≥15 years of age: Tablet: 10 mg tablet as least two hours before exercise; maximum, an additional dose should not be taken within 24 hours of a previous dose	
Zafirlukast	Asthma: Tablet: 20 mg two times daily	Asthma in patients 5 to 11 years of age: Tablet: 10 mg two times daily	Tablet: 10 mg 20 mg
Zileuton	Asthma: Sustained-release tablet: 1,200 mg twice daily Tablet: 600 mg four times daily	Asthma in patients ≥12 years of age: Sustained-release tablet: 1,200 mg twice daily Tablet: 600 mg four times daily	Sustained-release tablet: 600 mg Tablet: 600 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the leukotriene modifiers are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Leukotriene Modifiers

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Rhinitis				
Cingi et al.[16] (2010) Montelukast 10 mg QD vs placebo	DB, PC, RCT Patients with persistent allergic rhinitis	N=78 1 month	Primary: RQLQ Secondary: Not reported	Primary: A significant improvement in the RQLQ was observed in the montelukast group compared to the placebo group (P<0.001). A significant improvement in the RQLQ compared to baseline was observed in both the montelukast group and the placebo group (P<0.001). The difference in change from baseline to the end of the first month was significant in favor of the montelukast group for sleep, practical problems, nasal problems and activities that had been limited by nose or eye symptoms and for overall score (P<0.001). Secondary: Not reported
Li et al.[17] (2009) Montelukast 5 or 10 mg QD vs placebo All patients were also administered fexofenadine 60 or 120 mg QD.	DB, PC, RCT Patients 6 to 18 years of age with persistent allergic rhinitis for at least two years not previously treated with LTRAs	N=44 26 weeks (2 week run-in, 16 week treatment phase and 8 weeks of follow-up)	Primary: Composite nasal symptom score Secondary: Adenoidal size, nasal and blood cytokine levels	Primary: Significant between-group differences were observed in daytime sneezing score, nighttime sneezing score and daytime composite score at week four of treatment (P≤0.013) (level of significance adjusted to P<0.016). Eventually patients in the placebo group would experience symptom relief but this took a longer time when compared to the montelukast group. No significant differences were observed between groups during the follow-up period. Secondary: No significant differences were observed between groups.
Esteitie et al.[18] (2010)	DB, PC, RCT Patients 18 to 55	N=54 4 weeks	Primary: RQLQ, nasal symptoms	Primary: No significant differences were observed between groups in RQLQ or nasal symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Montelukast 10 mg QD vs placebo All patients were also administered fluticasone nasal spray 200 µg daily.	years of age with symptoms of perennial allergic rhinitis		Secondary: Not reported	Secondary: Not reported
Pullerits et al.[19] (2002) Montelukast 10 mg QD vs fluticasone nasal spray 200 µg QD vs montelukast 10 mg QD and loratadine 10 mg QD vs placebo	DB, DD, PC, PG, RCT Patients 15 to 50 years with a diagnosis of allergic rhinitis during the grass pollen season for at least the two previous years	N=62 50 days	Primary: Daytime and nighttime nasal symptom score as reported by patient (analysis divided into three periods: weeks one to two [period 1], weeks three to five [period 2] and week six to end of study [period 3]) Secondary: EG^{2+} eosinophilic inflammation	Primary: No statistically significant differences were noted in any of the primary endpoints between montelukast monotherapy and placebo. A significant decrease in the development of nasal allergy symptoms in both the fluticasone and the montelukast and loratadine groups compared to the placebo group during all three treatment periods for daytime symptoms was reported for period 1 (fluticasone; P=0.003, montelukast and loratadine; P=0.04), period 2 (fluticasone; P=0.001, montelukast and loratadine; P=0.04) and period 3 (fluticasone; P<0.001, montelukast and loratadine; P<0.001). No statistically significant differences in the fluticasone group and the montelukast and loratadine group in daytime nasal symptom scores were reported. A statistically significant decrease in development of nasal symptoms in the fluticasone group was reported compared to the montelukast monotherapy group (P=0.046). A statistically significant decrease in the development of nasal symptoms in the montelukast monotherapy group was observed compared to the placebo group (P=0.03). Significantly lower symptom scores in the fluticasone group was observed compared to the placebo group in all periods (P=0.02, P=0.002, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P<0.001 respectively). Significantly lower symptom scores in the fluticasone group were reported compared to the montelukast plus loratadine group during peak season in period 2 (P=0.04). Significantly lower symptom scores in the fluticasone group compared to the montelukast monotherapy group during periods 2 and 3 were observed (P=0.01). Significantly lower symptom scores in the montelukast plus loratadine group compared to the placebo group during period 3 were reported (P=0.02). Secondary: A statistically significant increase in EG^{2+} eosinophils in the placebo, montelukast monotherapy and montelukast plus loratadine groups was observed (P<0.01 for all groups). There was no significant increase in EG^{2+} eosinophils in the fluticasone group (P=0.2).
Baena-Cagnani et al.[20] (2003) Montelukast 10 mg QD vs desloratadine 5 mg QD vs placebo	DB, PC, RCT Patients 15 to 75 years of age diagnosed with seasonal allergic rhinitis for at least two years, clinical symptoms of seasonal allergic rhinitis at screening, $FEV_1 \geq 70\%$ predicted value, asthma controlled with as-needed bronchodilators	N=924 4 weeks	Primary: Total asthma symptom score, individual asthma symptom scores, FEV_1, PEF values and use of β_2-agonists Secondary: Not reported	Primary: A statistically significant reduction in the total asthma symptom scores in both the montelukast and desloratadine groups compared to the placebo group was observed (P≤0.05). No statistically significant differences between montelukast and desloratadine groups were noted at any time during the study for total asthma symptom scores. A statistically significant reduction in individual symptom scores in both the montelukast and desloratadine groups compared to the placebo group was reported (P<0.05). No statistically significant differences between montelukast and desloratadine groups were noted at any time during the study for individual asthma symptom scores.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	only, increase in FEV_1 of at least 12% following bronchodilator use, greater than weekly but no daily asthma symptoms and/or bronchodilator use and positive skin test for seasonal allergen			A statistically significant increase in FEV_1 in both the montelukast and desloratadine groups was reported compared to the placebo group ($P<0.01$ and $P<0.05$ respectively). There was no statistically significant difference between the montelukast and desloratadine groups at any time. Secondary: Not reported
Saengpanich et al.[21] (2003) Montelukast 10 mg QD and loratadine 10 mg QD vs fluticasone nasal spray 200 µg QD	DB, DD, PG, RCT Patients 21 to 54 years of age with history of sensitivity to ragweed pollen for last two years, and had a positive skin test to ragweed pollen	N=63 2 weeks	Primary: RQLQ, daily nasal symptom scores, number of eosinophils, and level of ECP found in nasal lavage fluids Secondary: Not reported	Primary: A statistically significant improvement in questionnaire answers in both the fluticasone and montelukast and loratadine groups was observed ($P<0.01$). A statistically significant reduction in nasal symptoms on the questionnaire in the fluticasone group compared to montelukast and loratadine group was observed ($P=0.05$). There was no statistically significant decrease in daily nasal symptom scores in either the fluticasone or montelukast and loratadine groups, though both did decrease from baseline. There was a statistically significant decrease in number of eosinophils in nasal lavage in the fluticasone group compared to baseline ($P=0.05$), though no significant decrease in the montelukast and loratadine group compared to baseline. When compared between groups, this was not statistically significant. A statistically significant decrease in ECP from baseline ($P=0.009$) and between groups ($P=0.04$) favoring fluticasone was observed. Secondary: Not reported
Meltzer et al.[22] (2000)	DB, MC, PC, PG, RCT	N=460	Primary: Daytime nasal	Primary: A statistically significant improvement in daytime nasal symptom scores

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Montelukast 10 to 20 mg QD vs loratadine 10 mg QD vs montelukast 10 mg QD and loratadine 10 mg QD vs placebo	Patients 15 to 75 years of age diagnosed with spring seasonal allergic rhinitis for two years, positive skin test for at least one of eight allergens including oak, grass, elm, olive, walnut and sycamore	2 weeks	symptoms score Secondary: Eye symptoms, nighttime symptoms, individual daytime symptoms, global evaluations and rhinoconjunctivitis quality of life scores	in the montelukast and loratadine group compared to placebo and to either agent alone was observed (P<0.001). A statistically significant improvement in all secondary endpoints in the montelukast plus loratadine group was reported compared to the placebo group (P<0.05). There was no statistically significant difference in the primary endpoint between montelukast or loratadine monotherapy groups compared to the placebo group. Secondary: A statistically significant improvement in rhinoconjunctivitis quality of life was reported in the montelukast 10 mg and loratadine group compared to the placebo group (P<0.05). A statistically significant improvement in daytime eye symptom score, nighttime symptom score, and composite daytime and nighttime symptom score was reported in the montelukast 10 mg monotherapy group compared to the placebo group (P<0.05).
Mucha et al.[23] (2006) Montelukast 10 mg QD vs pseudoephedrine 240 mg QD	DB, PG, RCT Patients 18 to 45 years of age with a diagnosis of allergic rhinitis during the ragweed season and a positive skin test to ragweed antigen extract	N=58 2 weeks	Primary: Nasal symptoms, NPIF, quality of life scores and tolerability profiles Secondary: Not reported	Primary: A statistically significant improvement in all primary outcome measures in both groups compared to baseline values (P<0.05) was observed. A statistically significant improvement was reported in nasal congestion in the pseudoephedrine group compared to the montelukast group (P=0.01). Secondary: Not reported
Sardana et al.[24] (2010) Montelukast 10 mg QD for 2 weeks	DB, PC, RCT, XO Patients 18 to 55 years of age with perennial allergic rhinitis	N=56 8 weeks	Primary: Changes in RSS Secondary: Not reported	Primary: Patients receiving montelukast experienced a significantly greater reduction in symptoms of itchy/watery eyes and itchy nose/throat/palate/ears compared to those receiving budesonide (P=0.0297 and P=0.0010, respectively). Patients receiving azelastine experienced a significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 28 µg 2 sprays BID for 2 weeks vs azelastine 137 µg 2 sprays BID for 2 weeks				improvement in rhinorrhea compared to montelukast (P=0.0044) and budesonide (P=0.0033). Secondary: Not reported
Jiang et al.[25] (2006) Zafirlukast 20 mg BID vs loratadine 10 mg QD vs loratadine 5 mg and pseudoephedrine 120 mg BID	RCT Patients 15 to 70 years of age with at least a 2 year history of perennial allergic rhinitis	N=93 14 days	Primary: Subjective assessment of nasal symptoms Secondary: Objective assessment via rhinomanometry and acoustic rhinometry, performed 1 day before first dose and within 2 days after last dose on same day as nasal symptom scoring	Primary: All treatment groups demonstrated a lower mean score for rhinorrhea, nasal itching and nasal obstruction (P<0.05). Patients who took zafirlukast did not report a significant decrease in sneezing score (P=0.1456), but the decrease in nasal obstruction score was more pronounced than in those who took loratadine or loratadine-pseudoephedrine (P=0.014). Secondary: Results of rhinomanometry and acoustic rhinometry showed no significant difference among the three groups (P>0.05).
Asthma				
Virchow et al.[26] (2010) MONICA Montelukast 10 mg QD Therapy added to	OL, OS, PRO Patients ≥18 years of age with mild or moderate persistent asthma insufficiently controlled with ICS	N=1,681 6 months	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved compared to baseline (P<0.0001). The percentage of patients with uncontrolled or poorly controlled asthma at baseline decreased. The percentage of patients with well-controlled or completely controlled asthma increased.

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current therapy with ICS or ICS and LABA.	or ICS and LABA			Secondary: Significant improvement in the Mini-AQLQ was observed from baseline (P<0.0001). Significant improvements in FEV_1 were observed from baseline (P<0.0001).
Virchow et al.[27] (2010) MONICA Montelukast 10 mg QD Therapy added to current therapy with ICS or ICS and LABA.	Subgroup analysis Patients ≥18 years of age with mild or moderate persistent asthma insufficiently controlled with ICS or ICS and LABA	N=1,681 12 months (additional 6 month follow-up after original MONICA)	Primary: ACT scores Secondary: Mini-AQLQ	Primary: Mean ACT score significantly improved at 12 months compared to baseline (P<0.0001). Secondary: Mean total Mini-AQLQ score increased significantly at 12 months compared to baseline (P<0.0001). Asthma control improved in all patient subgroups (gender, age [<30, 30 to 50, >50 years of age], duration of asthma [<5 years, ≥5 years], presence of allergic rhinitis, prior therapy with ICS or LABA and ICS). Comorbid allergic rhinitis, younger age, shorter duration of asthma and prior treatment with only ICS were indicators of better control with add-on montelukast.
Knorr et al.[28] (1998) Montelukast 5 mg QD vs placebo	DB, MC, PC, RCT Patients 6 to 14 years of age with asthma, FEV_1 between 50%-85% of predicted value, ≥15% reversibility after inhaled β-agonist therapy, daytime asthma symptoms, and reported daily β-agonist use	N=336 8 weeks	Primary: Improvements in morning FEV_1 Secondary: Daytime asthma symptoms, morning and evening PEF, daily use of inhaled short-acting β-agonists, nocturnal awakenings, pediatric asthma-specific quality of	Primary: A significant improvement in percent change from baseline in FEV_1 was reported in patients in the montelukast group compared to the placebo group (P<0.001). Secondary: A significant improvement in daily use of β-agonists was observed in the montelukast group (P=0.01). Significant improvements in percentage of days and percentage of patients experiencing asthma exacerbations were reported in the montelukast group (P=0.049). A significant improvement in the pediatric asthma-specific quality of life questionnaire was noted in the montelukast group (symptoms; P=0.007,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			life questionnaire, global evaluations, changes in blood eosinophil count, school absences, asthma exacerbations, use of oral corticosteroids, discontinuations because of worsening of asthma, asthma control days	activity; P=0.001, emotions; P=0.002). A significant improvement in parental (P=0.049) and combined (P=0.04) global evaluations were observed in the montelukast group. A significant improvement in morning clinic-measured PEF was reported in the montelukast group (P=0.03). A significant decrease in blood eosinophil levels over 8 weeks was observed in the montelukast group (P=0.02). Other secondary endpoints did not reach statistical significance because the study was not powered appropriately to detect a difference.
Reiss et al.[29] (1998) Montelukast 10 mg QD vs placebo Patients could also use ICS.	DB, MC, PC, RCT Patients 15 to 79 years with chronic stable asthma, FEV_1 50 to 85% predicted value, 15% or better improvement of FEV_1 after β-agonist, minimum level of daytime asthma symptoms, and use of an inhaled β-agonist	N=681 12 weeks	Primary: Percent change in FEV_1 from baseline and daytime asthma symptom score Secondary: Morning and evening PEF, daily use of inhaled short-acting β-agonists, number of nocturnal awakenings per week, asthma-specific quality of life, global assessment, blood eosinophil count, percentage of days with asthma exacerbation, use	Primary: There was a significant improvement in the percent change from baseline in FEV_1 with montelukast group compared to placebo (P<0.001). Secondary: A significant improvement in AM and PM PEF was reported in the montelukast group compared to placebo (P<0.001). A significant improvement in daytime asthma symptoms and β-agonist use was observed in the montelukast group compared to placebo (P<0.001). Improvement in nocturnal awakenings was observed in the montelukast group. A significant improvement in asthma specific quality of life questionnaire was reported in the montelukast group compared to placebo (P≤0.001). A significant improvement in global assessments was observed in the montelukast group compared to placebo (P<0.001). A significant improvement in days without asthma exacerbations and days with asthma control was reported in the montelukast group compared to placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of oral corticosteroids, discontinuation because of worsening of asthma, and asthma control days	A significant improvement in blood eosinophil count was observed in the montelukast group compared to placebo (P<0.001). The remainder of secondary endpoints (use of oral corticosteroids and discontinuation due to worsening of asthma) were not significantly different between the montelukast group and the placebo group.
Visitsunthorn et al.[30] (2011) Montelukast 5 mg QD vs placebo The use of ICS during study was permitted.	DB, PC, RCT, XO Patients 6 to 13 years of age with mild to moderate, persistent asthma	N=29 14 weeks (6 weeks with each treatment phase separated by a 2-week wash-out period)	Primary: Changes in FEV_1, FEV_1/FVC, PEFR and results of methacholine challenge test Secondary: Not reported	Primary: At six weeks, patients treated with montelukast had an increase in FEV_1 by 6.68 L/min, compared to a decrease by 2.74 L/min in patients treated with placebo (P=0.042). Similarly, FEV_1/FVC increased by 2.18% with montelukast and decreased by 3.18% with placebo (P=0.018). Improvement in PEFR was 25.05 L/min with montelukast and 0.12 L/min with placebo (P=0.63). The mean provocative concentration of methacholine that causes a 20% decline in FEV_1 was 6.8±1.74 and 5.7±1.41 mg/mL after six weeks of treatment with montelukast and placebo, respectively (P=0.79). Secondary: Not reported
Bozek et al.[31] (2012) Montelukast 10 mg QD vs placebo All patients were receiving budesonide 1,400 to 2,800 µg/day and salmeterol 50	OL, PRO, RCT Patients >60 years of age with severe asthma	N=512 24 months	Primary: Percentage of days without asthma symptoms Secondary: Compliance with therapy, average percentage of days with β_2-agonist use, change from baseline in pre-bronchodilator percent predicted FEV_1 and asthma	Primary: Patients in the montelukast group had a higher percentage of days without asthma symptoms compared to those in the placebo group (78.4 vs 66.2%; P<0.05). Secondary: Mean compliance was 80.1% in the montelukast group and 73.1% in the placebo group. Percentage of days with β_2-agonist use was 39.5 and 44.1% in the montelukast and placebo groups, respectively (P<0.05). FEV_1 percent predicted was similar in the montelukast and placebo groups (72.1 vs 71.5%; P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg BID.			exacerbations per year	One or more asthma exacerbations per year were observed in 30.2 and 38.4% of patients in the montelukast and placebo groups, respectively (P value not reported). The median number of asthma exacerbations per patient was 1.2 and 1.4, respectively (P value not reported).
Riccioni et al.[32] (2004) Montelukast 10 mg QD vs zafirlukast 40 mg/day	PG, RCT Adults with mild persistent asthma	N=40 12 weeks	Primary: FEV_1, FVC, PEF, use of rescue medications, AQLQ Secondary: Not reported	Primary: The values of the respiratory tests did not show statistical differences between the two agents. Statistically significant differences were seen with each groups baseline value compared with post-treatment (P<0.05). The amount of times that a rescue medication needed to be used was not statistically different (25 times for the montelukast vs 27 times for the zafirlukast group; P value not reported). There was no difference in quality of life between montelukast and zafirlukast: overall AQLQ (5.5 vs 5.7, P value not reported); symptoms (5.7 vs 5.6; P value not reported); environment (5.3 vs 5.6; P value not reported), emotions (5.3 vs 5.8; P value not reported), and activities (5.9 compared with 5.7; P value not reported). Secondary: Not reported
Kubavat et al.[33] (2013) Montelukast 10 mg QD vs zileuton ER 1200 mg BID	AC, MC, OL, RCT Patients 18 to 65 years of age with an established diagnosis of mild to moderate chronic persistent bronchial asthma	N=227 12 weeks	Primary: Improvement in PEFR Secondary: Improvement in respiratory symptom scores	Primary: Improvement in PEFR was significantly better in the zileuton group at the time points of 8 and 12 weeks as compared with the montelukast group (P<0.01 for both). The mean percent increase in PEFR at the end of 12 weeks' treatment was 27.0 ± 23.6% (22.6 to 31.5%) with zileuton and 18.4 ± 22.0% (14.1 to 22.7%) with montelukast (P=0.006). Secondary: Improvements occurred in all the assessed symptoms during the initial four weeks of therapy and further decreased in severity during the rest of the treatment period. A decline in rescue medication usage was noted in both the groups at the end of study as compared with the baseline; with no significant difference between the treatment groups. At the end of the study (week 12), as per the investigators' assessment of global efficacy of the study medication in the zileuton group, 95/109

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				[87.2% (80.9 to 93.4%)] patients were rated to have an ‘‘excellent’’ or a ‘‘good’’ efficacy as compared with 64 of 101 [63.4% (54.0 to 72.8%)] patients in the montelukast group (P<0.001).
Stelmach et al.[34] (2016) Ciclesonide 160 µg inhaled QAM and montelukast 5 mg or 10 mg PO QPM vs ciclesonide 160 µg inhaled QAM and formoterol 4.5 µg inhaled QAM and QPM vs ciclesonide 160 µg inhaled QAM vs ciclesonide 320 µg inhaled QAM	DB, PC, PRO, RC Children ages 12 to 18 years of age with a diagnosis of asthma and postexercise symptoms in the past 6 months despite chronic ICS treatment	N=80 8 weeks	Primary: Clinical symptoms as measured by a daily diary card. Secondary: Maximum percentage decrease in FEV_1 after exercise and FeNO in exhaled breath after exercise.	Primary: A significant decrease in daytime symptoms from baseline was seen in all groups except the ciclesonide + montelukast group. Mean daily symptoms were scored from 0 points (minimum) to 3 points (maximum). The median daytime symptom scores at baseline verses post study were 0.29 vs 0.19 in the ciclesonide 160 µg group (P=0.0303), 0.57 vs 0.26 in the ciclesonide 320 µg group (P=0.0084), 0.64 vs 0.29 in the ciclesonide + montelukast group (P=0.1213), and 0.43 vs 0.21 in the ciclesonide + formoterol group (P=0.0463). No statistically significant improvement in nighttime symptoms was observed in any of the treatment groups. Secondary: The change from baseline in the maximum decrease in FEV_1 reached the level of significance in all groups except the ciclesonide 160 µg group. The change from baseline in post-exercise FeNO only achieved significance in the ciclesonide 320 µg group.
Szefler et al.[35] (2005) Montelukast 5 to 10 mg QD vs fluticasone 100 µg	MC, RCT, XO Patients 6 to17 years of age with mild to moderate persistent asthma, asthma symptoms or rescue bronchodilator use	N=144 16 weeks	Primary: Percent change in pre-bronchodilator FEV_1 from baseline Secondary: Not reported	Primary: A significantly greater percent change in FEV_1 from baseline in the fluticasone group was reported compared to the montelukast group (P<0.001). Seventeen percent of patients responded to both treatments, 23% responded to fluticasone alone, 5% responded to montelukast alone and 55% responded to neither medication. Children with low pulmonary function or high levels of markers associated with allergic inflammation

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID	on average ≥3 days/week for past 4 weeks, reversibility defined as ≥12% improvement in FEV_1 after maximum bronchodilation or 20% improvement in FEV_1 after methacholine dose of ≤12.5 mg/mL and FEV_1 70% of predicted value or greater			responded better to the ICS than to montelukast. Secondary: Not reported
Zeiger et al.[36] (2006) Montelukast 5 to 10 mg QD vs fluticasone 100 µg BID	Post-hoc analysis Patients 6 to 17 years of age with mild to moderate persistent asthma, >12% improvement in FEV_1 after maximum bronchodilation or 20% improvement in FEV_1 after methacholine dose of ≤12.5 mg/ml, and FEV_1 ≥70% of predicted value	N=144 16 weeks	Primary: Asthma control days Secondary: Pulmonary function as measured by eNO, FEV_1 and FEV_1/FVC, resistance of the respiratory system at 5 Hz and area of reactance	Primary: Significant improvements in asthma control days were reported compared to baseline in both groups (P<0.001). A significant improvement in asthma control days in the fluticasone group was reported compared to the montelukast group (P<0.001). Secondary: A significant decrease in eNO in both groups was reported compared to baseline (P<0.001), and the difference between groups was significant, favoring fluticasone (P=0.028). Significant improvements were noted in both groups in FEV_1, FEV_1/FVC, resistance of the respiratory system at 5 Hz, and area of reactance compared to baseline.
Garcia et al.[37] (2005) Montelukast 5 mg QD	DB, NI, RCT Patients 6 to 14 years of age with mild persistent asthma, FEV_1 ≥80%	N=994 12 months	Primary: Percent of asthma rescue-free days measured as change from baseline	Primary: Montelukast was shown to be equivalent to fluticasone in percentage of asthma rescue-free days. Secondary: A significant difference in change from baseline in percentage of predicted

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vs fluticasone 100 µg BID	predicted value with β_2-agonist withheld ≥6 hours at least twice in run in period and FEV_1 or PEF ≥70% predicted value at visit 3		Secondary: Percentage change from baseline in predicted FEV_1, percentage of patients requiring anti-asthma medications other than β_2-agonists, percentage of patients with an asthma attack, average percentage of days with β_2-agonist use, change in blood eosinophil count, patient reports of asthma control, patient lost school days and parental lost work days	FEV_1 favoring fluticasone was observed (P=0.04). No significant difference in change from baseline in FEV_1 between the fluticasone group and montelukast group was observed. There was a significant difference in percentage of β_2-agonist use from baseline in both groups (P≤0.001). A significant decrease in percentage of β_2-agonist use in the fluticasone group was reported compared to the montelukast group (P=0.003). Significantly fewer patients in the fluticasone group used rescue asthma medications other than β_2-agonists compared to the montelukast group (P value not reported). Significantly fewer patients in the fluticasone group experienced an asthma attack compared to the montelukast group (P value not reported). There was no significant difference in the proportion of patients experiencing an asthma attack between the fluticasone group and montelukast group when analyzing only the patients who received no systemic corticosteroids during the previous year (P value not reported). A significant improvement in overall quality of life from baseline in both fluticasone and montelukast groups was reported (P≤0.001). A significant decrease in blood eosinophil count was reported in both fluticasone and montelukast groups from baseline (P≤0.001). There was a significant improvement in patient asthma control from baseline in both the fluticasone and montelukast groups (P≤0.001) though between-group comparison favored fluticasone (P value not reported). The proportion of patients with at least one lost school day during the four weeks preceding the 12 month visit was 8.8% in the montelukast group and 6.2% in the fluticasone group. The percentage of patients who lost >3 school days was 1.9% in the montelukast group and 2.1% in the fluticasone group. A at least one lost work day was reported in parents of

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				2.9% of montelukast patients and 2.0% of fluticasone patients during the four weeks prior to the 12 month visit, and the percentage whose parents lost >3 work days were reported as 0.4% in the montelukast group and 0.2% in the fluticasone group. The significance of these differences was not reported.
Busse et al.[38] (2001) Montelukast 10 mg QD vs fluticasone 44 µg BID	DB, DD, PG, RCT Patients 15 to 83 years of age diagnosed with asthma for at least six months, pre-bronchodilator FEV_1 between 50 to 80% of predicted value, increase in FEV_1 of 15% or greater after β_2-agonist use, regular or as-needed use of inhaled or oral β_2-agonist in the three months prior to screening	N=533 24 weeks	Primary: Mean percentage change from baseline in morning pre-medication FEV_1 Secondary: Mean change in FVC, $FEF_{25\%-75\%}$, morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings, daily rescue albuterol use, percentage of rescue-free days, physicians' global assessment of effectiveness, asthma quality of life questionnaire and patient-rated satisfaction with treatment	Primary: A significantly greater improvement in FEV_1 in the fluticasone group was reported compared to the montelukast group ($P \leq 0.002$). Secondary: A significantly greater improvement in all spirometric values in the fluticasone group was reported compared to the montelukast group ($P \leq 0.002$). A significant improvement in asthma symptom-free days in the fluticasone group was reported compared to the montelukast group ($P<0.001$). A significant improvement in asthma symptom scores in the fluticasone group was observed compared to the montelukast group ($P<0.001$). A significant improvement in nighttime awakenings in the fluticasone group was observed compared to the montelukast group ($P=0.023$). A significant improvement in rescue albuterol use in the fluticasone group was observed compared to the montelukast group ($P<0.001$). The physician's global assessment significantly favored fluticasone compared to montelukast ($P<0.001$). Significantly greater improvements was noted on the asthma quality of life questionnaire in the fluticasone group compared to the montelukast group ($P \leq 0.001$). Patient-rated satisfaction with treatment significantly favored the fluticasone group compared to the montelukast group ($P<0.001$).
Peters et al.[39] (2007)	DB, MC, RCT	N=500	Primary: Time to treatment	Primary: The rates of treatment failure were 20.2% in the fluticasone group, 20.4%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
LOCSS Montelukast 5 to 10 mg QD vs fluticasone 100 µg BID vs fluticasone-salmeterol 100-50 µg QD (fixed-dose combination product)	Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator, reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/ml within the previous 2 years. Patients were stable on fluticasone 100 µg BID and step-down therapy was being attempted.	16 weeks	failure Secondary: Measures of pulmonary function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	in the fluticasone and salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary: Mean pre bronchodilator FEV_1 values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone and salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the ACQ, was better in the fluticasone group and in the fluticasone and salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone and salmeterol group (22.9 vs 17.1%; P=0.06) and in the fluticasone group (22.9 vs 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone group than in the montelukast group (16.7 vs 25.4%; P=0.04), with a similar trend in the fluticasone and salmeterol group (17.3 vs 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6 to 85.8%.
Sorkness et al.[40] (2007) Montelukast 5 mg QD vs fluticasone 100 µg BID vs	DB, RCT Patients ages 6 to 14 years of age with mild-moderate persistent asthma, with an FEV_1 of ≥80% predicted normal at screening and ≥70% predicted normal at randomization	N=285 48 weeks	Primary: The percent of asthma control days Secondary: Percent of episode-free days, time to first exacerbation requiring prednisone, time to treatment failure,	Primary: The percent of asthma control days were 64.2% for the fluticasone monotherapy group, 59.6% for the fluticasone and salmeterol group and 52.5% for the montelukast group. The difference between the fluticasone monotherapy and the montelukast group was significant (P=0.004). The difference between the fluticasone and salmeterol group and montelukast was not significant (P=0.08). Secondary: The percent of episode-free days were 26.4% in the fluticasone group, 26.8% in the fluticasone and salmeterol group, and 17.8% in the montelukast group. The differences were significant between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)			number of treatment failures, ACQ score, FEV_1%, FEV_1/FVC, morning and evening PEF and growth	fluticasone group and the montelukast group (P=0.040) and between the fluticasone and salmeterol and montelukast groups (P=0.032). Kaplan-Meier survival curves showed significant "superiority" of fluticasone compared to montelukast monotherapy in favor of fluticasone in both time to first exacerbation requiring prednisone (P=0.002) and time to treatment failure (P=0.015). Twenty-eight total treatment failures occurred, five with fluticasone, eight with fluticasone and salmeterol and 15 with montelukast. The difference between fluticasone monotherapy and montelukast was significant (P=0.04). ACQ score improved by -0.69 in the fluticasone monotherapy group, -0.55 in the fluticasone and salmeterol group and by -0.45 in the montelukast group. There was no significant difference between the fluticasone monotherapy and fluticasone plus salmeterol therapy in ACQ score improvement; however, the difference between fluticasone monotherapy and montelukast was significant (P=0.018). The mean change in FEV_1 was 6.32% with fluticasone monotherapy, 3.62% with fluticasone and salmeterol and -0.58% with montelukast. The differences were significant between both the fluticasone monotherapy (P<0.001) and fluticasone and salmeterol (P=0.010) therapy when compared to montelukast. The mean change for FEV_1/FVC was 3.95% for the fluticasone monotherapy group, 1.76% for the fluticasone and salmeterol group and 0.07% for the montelukast group. The difference was significant between the fluticasone monotherapy group and montelukast (P<0.001). Morning PEF values improved by 5.18% in the fluticasone monotherapy group, 5.33% in the fluticasone and salmeterol group and by 0.65% in the montelukast group. The differences were significant between both the fluticasone monotherapy (P=0.002) and fluticasone and salmeterol (P=0.001) therapy when compared to montelukast.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Evening PEF values improved by 2.95% in the fluticasone monotherapy group, 4.31% in the fluticasone and salmeterol group and worsened by -0.57% in the montelukast group. The differences were significant between both the fluticasone monotherapy (P=0.017) and fluticasone and salmeterol (P<0.001) therapy when compared to montelukast. The mean increase height from baseline was 5.3 cm with fluticasone monotherapy and fluticasone and salmeterol. The increase in height was 5.7 cm in the montelukast group; however, the differences did not reach significance (P<0.001) for both groups compared to montelukast.
Calhoun et al.[41] (2001) Montelukast 10 mg QD vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)	DB, DD, MC, RCT Patients 15 to 72 years of age diagnosed with asthma for at least six months and had been treated with oral or inhaled β_2-agonists for at least six weeks prior to study, FEV_1 values of between 50 to 80% of predicted value and an increase in FEV_1 of at least 12% within 30 minutes of inhaled albuterol	N=423 12 weeks	Primary: Change from baseline in pre-dose FEV_1 values Secondary: Morning and evening PEF values, asthma symptom score, percentage of symptom-free days, β_2-agonist use, percentage of rescue-free days, percent of nights with no asthma-related awakenings, percentage of nights with no asthma-related awakenings in patients with ≥2 awakenings/week at baseline and nights/week with	Primary: A statistically significant improvement in the percent change from baseline in FEV_1 in the fluticasone and salmeterol group was observed compared to the montelukast group (P≤0.001). Secondary: A statistically significant improvement in all secondary endpoints for the fluticasone and salmeterol group was observed compared to the montelukast group (P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			no awakenings	
Maspero et al.[42] (2008) Montelukast 5 mg QD vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product)	DB, DD, MC, PG, RCT Patients 6 to 14 years of age with a diagnosis of asthma for ≥6 months, a FEV_1 between 55 to 80% of predicated normal with ≥12% FEV_1 reversibility and were not on any asthma control medications except for a SABA	N=548 12 weeks	Primary: Morning PEF values Secondary: FEV_1, evening PEF values, levels of symptoms and rescue medications, assessment of asthma control, asthma exacerbations, and safety	Primary: The mean change from baseline in morning PEF was 45.8 L/min in the fluticasone and salmeterol group, and 28.7 L/min in the montelukast group (P<0.001). Secondary: The mean change from baseline in evening PEF was 46.2 L/min in the fluticasone and salmeterol group, and 28.0 L/min in the montelukast group (P<0.001). The mean change from baseline in FEV_1 was 0.47 L in the fluticasone and salmeterol group, and 0.30 L in the montelukast group (P<0.001). The fluticasone and salmeterol group had significantly greater improvements in percentage of symptom free (P=0.025) and rescue free (P<0.001) 24-hour periods compared to the montelukast group. Asthma control was higher in the fluticasone and salmeterol group (88.3%) than in the montelukast group (66.7%; P<0.001). Twice as many patients in the montelukast group (23.2%) had asthma exacerbations than in the fluticasone and salmeterol group (10.3%). Fifty five percent of patients in the fluticasone and salmeterol group and 57% in the montelukast group reported an adverse event during treatment. The most common adverse event reported in both groups was headache (23% in the fluticasone and salmeterol group and 27% in the montelukast group).
Katial et al.[43] (2010) Montelukast 10 mg QD (MON) vs	DB, MC, PC, RCT Patients ≥15 years of age with asthma and a history of seasonal allergic rhinitis for at least two allergy seasons.	N=1,081 4 weeks	Primary: Mean change from baseline in AM PEF between FSC and FSC + MON, as well as FSC and MON	Primary: There was no significant difference in AM PEF between FSC and FSC+MON. The mean change from baseline in AM PEF was greater with FSC than MON (P<0.001). There was no significant difference between FSC+FPANS and FSC+MON with regards to AM PEF. There was no difference in AM PEF between FSC+FPANS and FSC monotherapy. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product) (FSC) vs fluticasone and salmeterol 100-50 µg BID (fixed-dose combination product) plus montelukast 10 mg QD (FSC+MON) vs fluticasone and salmeterol 100-50 µg BID and fluticasone nasal spray 200 µg QD (FSC+FPANS)	All patients were stabilized on either SABA, LABA, anticholinergic, cromolyn alone or in combination with an ICS for ≥1 month prior to study entry		Secondary: Changes in AM predose FEV_1, percent of symptom free days and albuterol free days, difference in D/N-TNSS	There was no significant difference in other asthma secondary endpoints between FSC and FSC+MON. FSC was significantly more effective than MON on other asthma secondary endpoints (percent symptom free days, percent albuterol free days, morning FEV_1, and PM PEF). There was no significant difference between FSC+FPANS and FSC+MON with regards to other asthma secondary endpoints. There was no difference in other asthma secondary endpoints between FSC+FPANS and FSC monotherapy. For rhinitis outcomes, FSC+FPANS was more effective than FSC+MON, with a mean change in D-TNSS of -3.1 vs -2.4, respectively (P<0.001) and a mean change in N-TNSS of -0.20 vs -1.7, respectively (P<0.001).
Fish et al.[44] (2001) Montelukast 10 mg QD vs salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients ≥15 years of age diagnosed with asthma remaining symptomatic despite therapy with a stable dose of ICS for the previous 30 days	N=948 12 weeks	Primary: Morning PEF values Secondary: Evening PEF, daytime asthma symptom score, supplemental albuterol use and nighttime awakenings	Primary: Significant increases in morning PEF in the salmeterol group were observed compared to the montelukast group (P<0.001). Secondary: A significant decrease in symptom scores in the salmeterol group was reported compared to the montelukast group (P=0.039). A significant decrease in supplemental albuterol use in the salmeterol group was reported compared to the montelukast group (P≤0.012). Significantly greater reductions in nighttime awakenings in the salmeterol group were reported compared to the montelukast group (P=0.015).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Yildirim et al.[45] (2004) Montelukast 10 mg QD and budesonide 400 µg/day vs budesonide 800 µg/day	PG, RCT Patients with moderate persistent asthma for minimum of six months who were admitted into the Department of Chest Diseases in Trabzon, Turkey	N=30 6 weeks	Primary: Morning, daytime and evening asthma symptoms, morning and evening PEF, FEV_1, blood eosinophil counts, frequency of SABA use and frequency of asthma exacerbations Secondary: Not reported	Primary: A significant decrease in morning and daytime symptom scores was reported in both groups compared to baseline scores ($P<0.05$), but no significant differences between the two groups were noted. No significant difference in evening symptom scores was reported in either group compared to baseline. No significant differences in FEV_1 or PEF values from baseline or between groups were reported. A significant decrease in blood eosinophil counts in both groups when compared to baseline ($P<0.05$) was reported, but there was no significant difference between the two groups. There was a significant decrease in β_2-agonist use in the budesonide plus montelukast group compared to baseline ($P<0.05$), but there was no significant difference in β_2-agonist use in the budesonide group compared to baseline. No patients in either group experienced an asthma exacerbation during the study period. Secondary: Not reported
Price et al.[46] (2003) Montelukast 10 mg QD and budesonide 800 µg/day vs budesonide 1,600 µg/day	DB, NI, PG, RCT Patients 15 to 75 years of age diagnosed with asthma not optimally controlled on regular ICS	N=889 12 weeks	Primary: Morning PEF values Secondary: Initial treatment effect on PEF (days one to three), daily self-reported β_2-agonist use, daytime symptoms, nocturnal	Primary: A significant improvement in morning PEF compared to baseline for both groups was reported ($P<0.001$) but differences between groups were insignificant at the end of the study. Secondary: The change from baseline in PEF during the first three days of treatment was significantly more rapid in the montelukast plus budesonide group compared to the budesonide group alone ($P<0.001$). All other secondary endpoints were not significantly different from baseline or between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			awakenings, asthma exacerbations, asthma-free days, blood eosinophil counts and asthma specific quality of life	
Bjermer et al.[47] (2003) Montelukast 10 mg QD and fluticasone 100 µg BID vs fluticasone 100 µg BID and salmeterol 50 µg BID	DB, DD, MC, PG, RCT Patients 15 to 72 years of age with chronic asthma ≥1 year, baseline FEV_1 50 to 90% predicted value, improvement of 12% or more in FEV_1 or in morning PEF after β_2-agonist use, regular use of ICS for at least 8 weeks prior to study and average β_2-agonist use of at least one puff/day	N=1,490 52 weeks	Primary: Percentage of patients with at least one asthma exacerbation Secondary: Asthma specific quality of life, nocturnal awakenings, mean FEV_1 before and after β_2-agonist use, mean morning PEF, time to first asthma exacerbation and blood eosinophil counts	Primary: No significant difference between the two groups in percentage of patients with at least one asthma attack was reported. Secondary: A significant improvement in asthma specific quality of life compared to baseline in both groups was reported (P≤0.001), though there was no significant difference between the two groups. A significant decrease in nocturnal awakenings from baseline in both groups was reported (P≤0.001), though there was no significant difference between the two groups. A significant improvement in FEV_1 before β_2-agonist use in the salmeterol and fluticasone group was observed compared to the montelukast and fluticasone group (P≤0.001), though the improvement in FEV_1 after β_2-agonist use was similar between the two groups. A significantly larger increase in morning PEF in the salmeterol and fluticasone group was reported compared to the montelukast and fluticasone group (P≤0.001), though both groups significantly improved morning PEF values from baseline (P≤0.001). No significant differences between the groups regarding time to first asthma exacerbation were observed. A significant decrease in blood eosinophils in the montelukast and fluticasone group was reported compared to the salmeterol and fluticasone group (P=0.011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lemanske et al.[48] (2010) BADGER Montelukast 5 to 10 mg QD and fluticasone 100 µg BID (LTRA step-up therapy) vs salmeterol 50 µg BID and fluticasone 100 µg BID (LABA step-up therapy) vs fluticasone 250 µg BID (ICS step-up therapy)	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma uncontrolled while receiving fluticasone 100 µg BID	N=182 48 weeks (three 16 week periods)	Primary: Differential response to each of the three step-up therapies based on control measures including requirement of oral prednisone for acute exacerbations, number of asthma control days and FEV_1 Secondary: Not reported	Primary: The response to LABA step-up therapy was significantly more likely to be the best response as compared to the response to LTRA step-up and ICS step-up therapy (P=0.004 and P=0.002 respectively). Secondary: Not reported
Suissa et al.[49] (1997) Zafirlukast 20 mg BID vs placebo	DB, MC, PC, RCT Patients ≥12 years of age, non-smokers in the last six months, smoking history of less than 10 pack-years, FEV_1 at least 55% of predicted value, with bronchial hyper-responsiveness and who were	N=146 13 weeks	Primary: Days without limitation of activity, days without use of β_2-agonists, days without episodes of asthma and days without sleep disturbance Secondary: Unscheduled health care visits	Primary: Significantly more days without asthma symptoms was observed in the zafirlukast group (P=0.03). Significantly more days without β_2-agonist use were observed in the zafirlukast group (P=0.001). Significantly more days without episodes of asthma were reported in the zafirlukast group (P=0.003). More days without sleep disturbances were reported in the zafirlukast group (P>0.2). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	symptomatic during the seven-day run-in period of the study		and contacts, total number of β_2-agonist inhalers used, number of prescriptions for non-asthma medications consumed and number of days absent from work or school	A significant decrease in health care contacts was reported in the zafirlukast group (P=0.007). A significant decrease in asthma-related absenteeism was reported in zafirlukast group (P=0.04). A decrease in canisters of β_2-agonists used was observed in the zafirlukast group (P=0.17). A decrease in the use of non-asthma medications was observed in the zafirlukast group (P>0.2).
Busse et al.[50] (1999) Zafirlukast 20 mg BID vs salmeterol 42 µg BID	DB, DD, MC, PG, RCT Patients 12 to 73 years of age with a diagnosis of asthma for ≥6 months; after the run-in period, patients were required to have FEV_1 values of 50 to 70% predicted value with or without symptoms or FEV_1 values of 70.1 to 80.0% predicted value with one or more of the following criteria: average of ≥4 puffs/ day of albuterol, symptom score ≥2 in any asthma symptom category on ≥2 days, ≥1 nighttime	N=289 4 weeks	Primary: Morning PEF values Secondary: Evening PEF values, asthma symptom scores, supplemental albuterol use, nighttime awakenings, FEV_1 and asthma exacerbations	Primary: A statistically significant improvement in morning PEF values in the salmeterol group was reported compared to the zafirlukast group (P=0.001). Secondary: A statistically significant improvement in evening PEF values in the salmeterol group was reported compared to the zafirlukast group (P=0.019). Statistically significant improvements in asthma symptom scores in the salmeterol group were reported compared to the zafirlukast group (P≤0.026). A statistically significant decrease in daytime and nighttime supplemental albuterol use in the salmeterol group was noted compared to the zafirlukast group (P=0.004 and P=0.013 respectively). No statistically significant difference in nighttime awakenings between the two groups was reported (P=0.142). A statistically significant improvement in FEV_1 compared to baseline in both groups was reported (P<0.001), but no statistically significant difference between groups at the end of the treatment period was observed (P=0.293).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	awakening due to asthma, or ≥2 days when evening to morning PEF values differed by ≥20%			Seven patients in the salmeterol group and nine patients in the zafirlukast group experienced asthma exacerbations during the treatment period (P values not reported).
Israel et al.[51] (1993) Zileuton 600 mg QID vs zileuton 800 mg BID vs placebo	DB, PC, RCT Patients 18 to 65 years of age with FEV_1 40 to 75% of predicted value, a 15% or greater increase in FEV_1 30 minutes after inhalation of albuterol and who were not being treated with inhaled or oral corticosteroids	N=139 4 weeks	Primary: FEV_1, asthma symptoms and frequency of β_2-agonist use Secondary: Not reported	Primary: There was a significant (14.6%) increase in FEV_1 within one hour in both zileuton groups compared to baseline (P<0.001). There was a significant change in FEV_1 in the zileuton 600 mg group after four weeks compared to the placebo group (P=0.02). There was a significant decrease in asthma symptoms in all three groups (P<0.01), but the change was the greatest in the zileuton 600 mg group compared to the placebo group (P=0.02). There was a significant decrease in β_2-agonist use in the zileuton 600 and 800 mg group (P<0.001 and P=0.005 respectively) from baseline. Compared to the placebo group, the change was only significant in the 600 mg group (P=0.03). Secondary: Not reported
Israel et al.[52] (1996) Zileuton 600 mg QID vs zileuton 400 mg QID vs	DB, PG, RCT Patients with mild to moderate asthma, FEV_1 40 to 80% of predicted value, only being treated with inhaled β_2-agonists	N=401 13 weeks	Primary: Frequency of asthma exacerbations requiring corticosteroid treatment, use of inhaled β_2-agonists, FEV_1, asthma symptoms and quality of life evaluations	Primary: There was a significantly lower percentage of patients requiring corticosteroid treatment in the zileuton 600 mg group compared to the placebo group (P=0.02). There was a significant increase in FEV_1 in the zileuton 600 mg group compared to the placebo group (P=0.006). There was a significant improvement in quality of life assessments in the zileuton group compared to the placebo group (P=0.007). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			Secondary: Not reported	
Wenzel et al.[53] (2007) Zileuton CR 1200 mg BID vs placebo	DB, MC, PC, RCT Patients ≥12 years of age and non-smoking for at least 6 months; ex-smokers with ≤10-pack year history of cigarette smoking; FEV_1 ≥40% predicted at least 48 hours after last theophylline use, at least 12 hours after long-acting β-agonist (salmeterol) use, and at least 6 hours after SABA use; ≥15%in FEV_1 at least 15 minutes after inhaled albuterol; and history of 15% reversibility documented within 1 year	N=926 6 months	Primary: Mean change in PEFs Secondary: Improvement in trough FEV1; change in number of daily doses of SABA; change from baseline in total score of Asthma quality of life questionnaire measured at three and six months	Primary: Sustained improvements in PEF were observed in the zileuton group compared to placebo. Secondary: Improvement in trough FEV_1 was similar between zileuton and placebo groups. There was no significant difference in the number of daily doses of SABA with zileuton compared to placebo. Treatment with zileuton resulted in greater mean improvements in quality of life than did treatment with placebo at six for the symptoms domain (0.74 vs 0.56, P=0.040) and the emotions domain (0.63 vs 0.42, P=0.043). The overall score improved by 0.71 for the zileuton group and 0.57 for the placebo group (P=0.083).
Nelson et al.[54] (2007) Zileuton CR 1,200 mg BID vs zileuton IR 600 mg	AC, DB, MC, PC, RCT Patients ≥12 years with moderate persistent asthma with an FEV_1 of 40 to 75% of predicted when taken ≥48	N=591 16 weeks	Primary: Change from baseline in morning trough FEV_1 Secondary: Percentage of patients with	Primary: At week 12, compared to the placebo CR group, the zileuton CR group demonstrated a significant mean improvement in FEV_1 (0.39 L [20.8%] vs 0.27 L [12.7%]; P=0.02). Compared to the placebo IR group, the zileuton IR group reported a non-significant improvement (0.38 L [19.3%] vs 0.28 L [14.1%]; P=0.19). Secondary: At week 12, 63.2% of the zileuton CR patients showed a 12.0% or greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QID vs placebo CR or placebo IR	hours after the last theophylline use and at least six hours after SABA use or 24 hours after LABA use who had not been hospitalized for asthma within six months		clinically significant improvement in lung function (≥12% in FEV_1), change from baseline in morning PEFR and reduction in the number of daily puffs of SABA, safety	improvement in FEV_1, compared to 50.0% in the placebo CR group. In the zileuton IR group 45.5% of patients had a 12.0% or great FEV_1 improvement, compared to 27.8% in the placebo IR group (P=0.02). However, this was only seen in the IR group at week four. The zileuton CR group reported an increasing mean improvement from baseline morning PEFR from 19.42 L/min for days two to 22 to 58.45 L/min for days 72 to 92. The difference between the zileuton CR group and the placebo CR group were not significant (P value not reported). Similar improvements were reported in the zileuton IR treatment group; however, the values were also not statistically significant. There was a 15.14% reduction from baseline of SABA use in the zileuton CR treatment grouped compared to a 2.29% reduction in the zileuton IR treatment group. The difference between the two groups was significant (P=0.009). The overall incidence of adverse events in the study was similar between all treatment groups (78.4% with zileuton CR, 76.8% with zileuton IR and 77.3% with placebo IR). The most common adverse events in the zileuton CR group were exacerbation of asthma, headache, sinusitis, nausea, nasopharyngitis and pharyngolaryngeal pain. Eight percent more patients in the placebo CR treatment group experienced asthma exacerbation that the zileuton CR group. Five out of 199 patients (2.5%) in the zileuton CR group and one out of 198 patients (0.5%) in the placebo CR group developed ALT level elevations of three times the upper limit of normal or greater. The investigators did not attribute the adverse events to the treatment medication. Two of the 97 patients (2.1%) in the zileuton IR group and one of the 97 patients (1.0%) in the placebo IR group developed ALT levels of three times the upper limit of normal or greater.
Exercise-Induced Bronchoconstriction				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wasfi et al.[55] (2011) Montelukast 4 or 5 mg for a single dose vs placebo Two exercise challenges were administered at two and 24 hours post-dose.	DB, PC, RCT, XO Patients 4 to 14 years of age with a history of exercised-induced bronchoconstriction or wheeze or shortness of breath with exercise as well as a preexercise FEV_1 ≥70% predicted and a maximum percent fall in postexercise FEV_1 ≥20% within 60 minutes	N=66 24 hours	Primary: Maximum percent fall from preexercise baseline in FEV_1 after exercise challenge at two hours post-dose Secondary: Maximum percent fall from preexercise FEV_1 after exercise challenge at 24 hours post-dose, AUC over the first 60 minutes for the percent fall from preexercise FEV_1, time to recovery of FEV_1 to within 5% of baseline, need for rescue medication, proportion of patients achieving maximum percent fall in FEV_1 ≤20% and safety	Primary: The mean maximum percent fall in FEV_1 at two hours post-dose was smaller in the montelukast group compared to the placebo group (15.35 vs 20.00%; P=0.02). Secondary: At 24 hours post-dose, the maximum percent fall in FEV_1 was significantly smaller with montelukast compared to placebo (12.92 vs 17.25%; P=0.005). The AUC over the first 60 minutes for the percent fall in FEV_1 was also significantly smaller with montelukast compared to placebo at two hours (294.50 vs 415.37 %*minute; P=0.022) and 24 hours post-dose (227.98 vs 350.80 %*minute; P=0.013). Time to recovery of FEV_1 to within 5% of baseline in the montelukast and placebo groups were 16.21 and 24.48 minutes, respectively, at two hours post-dose (P=0.064) and 11.49 and 18.55 minutes, respectively (P=0.054) 24 hours post-dose. The differences were not statistically significant. At two hours post-dose 1.6% of patients in the montelukast group and 3.1% in the placebo group required rescue medications after the exercise challenges (P=1.0). At 24 hours, 3.2% of patients in the placebo group and no one in the montelukast group required rescue medication (P value not reported). At two hours post-dose, the proportion of patients who had a maximum percent fall in FEV_1 ≤20% was 76.6 and 56.3% in the montelukast and placebo groups, respectively (P=0.015). At 24 hours, the proportion was 80.6 and 67.7%, respectively (P=0.077). In the montelukast group, proportion of patients who had a maximum percent fall in FEV_1 <10%, 10 to 20% and >20% at two hours was 26.6, 50.0 and 23.4%, respectively, at two hours and 45.2, 35.5 and 19.4%, respectively, at 24 hours. In the placebo group, the corresponding numbers were 25.0, 31.3 and 43.8%, respectively, at two hours (P=0.034) and 30.6, 37.1 and 32.3%, respectively, at 24 hours (P=0.061).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported in 6.2 and 7.6% of patients in the montelukast and place groups, respectively (P value not reported). No serious or drug-related adverse events were reported.
Philip et al.[56] (2007) Montelukast 10 mg vs salmeterol 50 µg vs placebo	DB, PC, RCT, XO Men and women who demonstrated a fall in FEV_1 following exercise (ΔFEV_1) of ≥20%	N=47 9 to 21 days	Primary: Maximum ΔFEV_1 observed after exercise challenge at two hours postdose for montelukast Secondary: Maximum ΔFEV_1 observed after the challenges at 8.5 and 24 hours postdose, recovery time and need for β-agonist rescue for montelukast	Primary and Secondary: Maximum ΔFEV_1 at 2.0, 8.5, and 24.0 hours were significantly smaller after montelukast administration than after placebo administration (least squares mean, 13.2±1.2, 11.7±1.2, and 10.0±1.1 vs 21.8±1.2, 16.8±1.3, and 14.0±1.1%, respectively; P≤0.001, P<0.01, and P<0.05). Montelukast and salmeterol had similar efficacy at 2.0 and 8.5 hours, but only montelukast was effective at 24 hours. Montelukast was associated with substantially less use of SABA rescue vs placebo at two hours postdose (P=0.031). Salmeterol vs placebo was accompanied by higher levels of FEV_1 before exercise, significant reductions in mean maximum ΔFEV_1, and fewer instances of SABA rescue.
Fogel et al.[57] (2010) Montelukast 5 mg QD vs salmeterol 50 µg BID All patients received OL fluticasone 50 µg 2 puffs BID throughout the study.	DB, MC, RCT, XO Patients 6 to 14 years of age with exercise-induced bronchoconstriction, FEV_1 ≥70%, who were receiving treatment with an ICS	N=154 8 weeks	Primary: Percent change in FEV_1 after exercise and before SABA administration Secondary: AUC for first 20 minutes after exercise, time to recovery within 5% of pre-exercise FEV_1, maximum FEV_1% predicted after SABA, average percent	Primary: Montelukast was significantly more effective than salmeterol for maximum percent decrease in FEV_1 after exercise (10.6 vs 13.8%; P=0.009) and for mean percent change after exercise. Montelukast provided significantly more effective broncho-protection than salmeterol as shown by a smaller $AUC_{0–20}$ (P=0.006) and a shorter time to recovery (P=0.04). Patients receiving montelukast had a significantly better response to SABA based on FEV_1 percent predicted (103.1 vs 100.9%; P<0.001). The average percent change in FEV_1 after SABA use was significantly greater in the montelukast group than the salmeterol group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			change from pre-exercise baseline FEV_1 after SABA	

Drug regimen abbreviations: BID=twice daily, CR=controlled-release, IR=immediate-release, QD=once daily, QID=four times daily
Study design abbreviations: AC=active comparator, DB=double blind, DD=double dummy, OL=open label, OS=observational, MC=multicenter, NI=non inferiority, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=cross over
Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, ACT=asthma control test, ALT=alanine aminotransferase, AUC=area under the curve, CI=confidence interval, D/N-TNNS=daytime and nighttime total nasal symptom score, ECP=eosinophil cationic protein, eNO=exhaled nitric oxide, FEV_1= forced expiratory volume in 1 second, FVC=forced vital capacity, HR=hazard ratio, ICS=intranasal corticosteroid, LABA=long-acting β_2-agonist, LTRA=leukotriene receptor antagonist, Mini-AQLQ=Mini Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, RQLQ=rhinoconjunctivitis quality of life questionnaire, SABA=short-acting β_2-agonist

Additional Evidence

Dose Simplification
Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids. Compared to patients receiving inhaled corticosteroids, patients receiving a leukotriene modifier were more likely to refill their prescriptions at least once during the first year of treatment (67.9 vs 52.7%), were less likely to discontinue treatment (relative risk, 0.46; 95% confidence interval, 0.85 to 0.98), and were more likely to be on treatment longer during the first year of therapy (38 vs 19%; P<0.001).[58]

Bukstein et al. evaluated preference with montelukast or inhaled cromolyn sodium in children with asthma. More parents (87 vs 12%, respectively; P<0.001) and children (82 vs 17%, respectively; P<0.001) preferred montelukast to cromolyn. Parents and children expressed greater overall satisfaction with montelukast compared with cromolyn (P<0.001). The most prevalent reason for greater parental satisfaction with montelukast stemmed from its greater convenience and ease in getting the child to use the medication, as well as less interference with the parent's lifestyle. Additionally, significantly more patients were adherent while taking montelukast than while taking cromolyn (78 vs 42%, respectively; P<0.001). The mean albuterol use during montelukast therapy was significantly lower than that reported during cromolyn therapy (1.56 vs 1.92, respectively; P=0.003).[59]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Suissa et al. demonstrated a significant reduction in health care resource utilization in patients taking zafirlukast compared to those taking placebo.[49] Price et al. found no difference in health care resource utilization with montelukast compared to budesonide in patients with asthma.[46]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Leukotriene Modifiers

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Montelukast	chewable tablet, granules, tablet	Singulair®*	$$$$$	$
Zafirlukast	tablet	Accolate®*	$$$$$	$$$
Zileuton	sustained-release tablet*, tablet	Zyflo®	$$$$$	$$$$$

*Generic available in at least one dosage form and/or strength.
N/A=Not available.

X. Conclusions

For the treatment of asthma, the 2021 Global Initiative for Asthma guidelines recommend the use of a daily low-dose inhaled corticosteroid or as-needed inhaled corticosteroid-formoterol combination treatment as initial therapy.[8] Due to the fact they the leukotriene modifiers are generally less effective compared to inhaled corticosteroids, they may be considered as an alternative treatment in patients with mild persistent asthma.[8-9] In addition, leukotriene modifiers may be used as an alternate controller option in patients less than five years of age who cannot receive inhaled corticosteroids.[8] Add-on leukotriene modifier therapy may reduce the dose of inhaled corticosteroids required in patients with moderate to severe asthma and improve asthma control. However, add-on leukotriene modifier therapy is not as effective as long-acting β_2-agonist add-on therapy; therefore, when a medium dose inhaled corticosteroid fails to achieve asthma control, the addition of a long-acting β_2-agonist is the preferred treatment.[8] Guidelines do not give preference to one leukotriene modifier over another for the treatment of asthma.[8-9]

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists, and mast cell stabilizers. When selecting an agent for the treatment of allergic rhinitis and conjunctivitis, clinicians should take into consideration the severity of symptoms, duration of disease, patient preference, as well as efficacy.[10-15] Intranasal corticosteroids are considered the most effective treatment for controlling symptoms of allergic rhinitis and should be considered first-line therapy in patients with moderate to severe symptoms.[13-15] Montelukast is recommended for adults and children with seasonal allergic rhinitis, and in pre-school children with persistent allergic rhinitis; however, montelukast has limited efficacy in adults with persistent allergic rhinitis.[10] Currently, montelukast is the only leukotriene modifier Food and Drug Administration (FDA)-approved for the treatment of allergic rhinitis and guidelines do not give preference to one leukotriene modifier over another.[3,10-15]

Clinical trials have demonstrated that the leukotriene modifiers improve asthma outcomes, including pulmonary function, daytime symptoms, nocturnal awakening, β_2-agonist use, exacerbations and quality of life. However, they have generally been shown to be less effective than inhaled corticosteroids and long-acting β_2-agonists.[26-54] There are limited head-to-head trials comparing the leukotriene modifiers for the treatment of asthma.[32,33]

Clinical trials have demonstrated that the leukotriene modifiers improve quality of life and symptom scores in patients with allergic rhinitis. In clinical trials, there was no difference in efficacy between montelukast and second-generation antihistamines; however, montelukast was found to be less effective than treatment with intranasal corticosteroids.[16-25]

Few clinical trials have demonstrated that montelukast is effective in the treatment of exercised-induced bronchocontstriction.[55-57] Currently, montelukast is the only leukotriene modifier FDA-approved for acute prevention of exercise-induced bronchoconstriction.[3]

There is insufficient evidence to support that one brand leukotriene modifier is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand leukotriene modifiers within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendation

No brand leukotriene modifier is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Inhaled Mast-Cell Stabilizers
AHFS Class 481032
August 10, 2022

I. Overview

Cromolyn sodium is the only inhaled mast-cell stabilizer that is currently available in this class. It is approved for the maintenance treatment of asthma, as well as for the prophylaxis of acute bronchospasm induced by exercise, exposure to cold air, or other environmental agents. Cromolyn sodium has no intrinsic bronchodilator or antihistaminic activity; however, it inhibits mast cell degranulation after exposure to antigens. It indirectly blocks calcium ions from entering the mast cell, which prevents the release of mediators and inhibits bronchoconstriction. Cromolyn sodium has been shown to reduce asthma symptoms, improve morning peak flow, and reduce the need for short-acting bronchodilators.[1-3]

The inhaled mast-cell stabilizers that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Cromolyn sodium inhalation solution is available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Inhaled Mast-Cell Stabilizers Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cromolyn sodium	inhalation solution*	N/A	cromolyn sodium

*Generic is available in at least one dosage form or strength.
N/A=Not available.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the inhaled mast-cell stabilizers are summarized in Table 2.

Table 2. Treatment Guidelines Using the Inhaled Mast-Cell Stabilizers

Clinical Guideline	Recommendations
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2021)**[16]	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified. • Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers. • Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources. • Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences. • For population-level decisions about asthma treatment, the 'preferred option' represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk. • For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.

Clinical Guideline	Recommendations
	Medications and strategies for symptom control and risk reduction • For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone. • This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms. • Choice of reliever o Low dose ICS-formoterol is the preferred approach recommended by this guideline. o SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy. • Mild asthma o Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death. o In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control. • Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique o Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities. ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium. ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age. ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA. ▪ For children, try other controller options at the same step before stepping up. ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. • Stepping down to find the minimum effective dose o Consider step down once good asthma control has been achieved and maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. • For all patients with asthma o Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect. o Encourage adherence with controller medication, even when symptoms are infrequent. o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations. o For patients with one or more risk factors for exacerbations:

Clinical Guideline	Recommendations
	▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function). ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies). • Difficult-to-treat and severe asthma o Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics. <u>Categories of asthma medications</u> • *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise. • *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment. • *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. <u>Initial controller treatment</u> • For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made. <u>Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u> • Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment. • If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment: o Incorrect inhaler technique. o Poor adherence. o Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs). o Comorbidities that may contribute to respiratory symptoms and poor quality of life. o Incorrect diagnosis.

Clinical Guideline	Recommendations

Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)

Controller and preferred reliever (Track 1)	**Steps 1 to 2** As-needed low dose ICS-formoterol		**Step 3** Low dose maintenance ICS-formoterol	**Step 4** Medium dose maintenance ICS-formoterol	**Step 5** Add-on LAMA Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
	Reliever: as-needed low-dose ICS-formoterol				
Controller and alternative reliever (Track 2)	**Step 1** Take ICS whenever SABA taken	**Step 2** Low dose maintenance ICS	**Step 3** Low dose maintenance ICS-LABA	**Step 4** Medium/high dose maintenance ICS-LABA	**Step 5** Add-on LAMA Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
	Reliever: as-needed SABA				

- Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

Personalized management to control symptoms and minimize future risk (six to 11 years of age)

	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller	Low dose ICS taken when SABA is taken	Daily low dose ICS	Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy	Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)
Other controller options	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken	Low dose ICS+LTRA	Add tiotropium, or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side effects
Reliever	As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)				

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak expiratory flow.

Clinical Guideline	Recommendations
	• For patients presenting with an exacerbation to a primary care or acute care facility: o Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. o Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given. o Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be reviewed after one hour. o Ipratropium bromide treatment is recommended only for severe exacerbations. o Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment. o Chest X-ray or prescribing antibiotics is not routinely recommended. o Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. o Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use. • Arrange early follow-up after any exacerbation, regardless of where it was managed. o Review the patient's symptom control and risk factors for further exacerbations. o Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks. o Provide a written asthma action plan and advice about avoiding exacerbation triggers. o Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> • The goals of asthma management in young children are similar to those in older patients: o To achieve good control of symptoms and maintain normal activity levels. o To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects. • Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective. • A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe. • Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis. • The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds. • Review the need for asthma treatment frequently, as asthma-like symptoms remit

Clinical Guideline	Recommendations

in many young children.

Personalized management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

Management of worsening asthma and exacerbations in children five and younger

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - There is no compelling evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%).
  - Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air.
  - Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days for children attending an emergency department or admitted to hospital, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone.
- Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma

Clinical Guideline	Recommendations
	management.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2019)[5]**	Pharmacological management • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%. • Intermittent reliever therapy: o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. o For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. o Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years of age with asthma. o ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: o In adults, the first choice add-on therapy to an ICS is a LABA, which should be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. o In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: o If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in

Clinical Guideline	Recommendations
	adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: o All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. o If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed) ▪ Add tiotropium (adults) ▪ Add a theophylline. o If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). o Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored. o Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. o Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. o The use of immunotherapy is not recommended for the treatment of asthma in adults or children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the inhaled mast-cell stabilizers are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Inhaled Mast-Cell Stabilizers[1]

Indication	Cromolyn Sodium
Asthma	
Management of patients with bronchial asthma	✔
Acute Bronchospasm	
Prophylaxis of acute bronchoconstriction in response to exercise, toluene diisocyanate, and environmental pollutants	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the inhaled mast-cell stabilizers are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Inhaled Mast-Cell Stabilizers[2]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (minutes)
Cromolyn sodium	8	63 to 76	Not metabolized	Renal (30 to 50) Feces (80 to 87)	80 to 90

V. Drug Interactions

There are no significant drug interactions with the inhaled mast-cell stabilizers.[1,2]

VI. Adverse Drug Events

The most common adverse drug events reported with the inhaled mast-cell stabilizers are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Inhaled Mast-Cell Stabilizers[1,2]

Adverse Events	Cromolyn Sodium
Cardiovascular	
Pericarditis	<1
Central Nervous System	
Dizziness	<1
Drowsiness	✔
Headache	<1
Vertigo	<1
Dermatological	
Exfoliative dermatitis	<1
Photodermatitis	<1
Rash	<1
Urticaria	<1
Gastrointestinal	
Dyspepsia	✔
Nausea	<1
Genitourinary	
Dysuria	<1
Urinary frequency	<1
Musculoskeletal	
Joint swelling and pain	<1
Myalgia	<1
Polymyositis	<1
Respiratory	
Bronchospasm	<1
Cough	<1
Epistaxis	✔
Hoarseness	<1
Nasal burning	✔
Nasal congestion	<1
Nasal itching	✔
Pulmonary infiltrates with eosinophilia	<1
Sneezing	✔
Wheezing	✔
Other	
Anaphylaxis	<1
Anemia	<1
Angioedema	<1

Adverse Events	Cromolyn Sodium
Hemoptysis	<1
Lacrimation	<1
Laryngeal edema	<1
Nephrosis	<1
Peripheral neuritis	<1
Parotid gland swelling	<1
Serum sickness	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the inhaled mast-cell stabilizers are listed in Table 6.

Table 6. Usual Dosing Regimens for the Inhaled Mast-Cell Stabilizers[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cromolyn sodium	Asthma: Inhalation solution: 20 mg four times daily Bronchospasm prophylaxis: Inhalation solution: 20 mg administered shortly before exposure to the precipitating factor	Asthma in patients ≥2 years of age: Inhalation solution: 20 mg four times daily Bronchospasm prophylaxis in patients ≥2 years of age: Inhalation solution: 20 mg administered shortly before exposure to the precipitating factor	Inhalation solution: 20 mg/2 mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the inhaled mast-cell stabilizers are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Inhaled Mast-Cell Stabilizers

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Leflein et al.[6] (2002) Cromolyn sodium 20 mg QID via nebulization for 8 weeks, followed by dose titration vs budesonide 0.5 mg/day via nebulization for 8 weeks, followed by dose titration	MC, OL, PG, RCT Children 2 to 6 years of age with persistent asthma treated with at least one long-term control medication, but no long-term or intermittent oral corticosteroids within 12 weeks and 15 days, respectively, of study entry	N=335 52 weeks	Primary: Rate of asthma exacerbations Secondary: Time to first asthma exacerbation, first use of additional asthma therapy, asthma symptom score, rescue medication use, health-care resource use, change in height standard deviation scores	Primary: Treatment with budesonide inhalation suspension significantly reduced the rate of asthma exacerbations per year compared with cromolyn sodium nebulizer solution (P<0.001). The mean exacerbation rate for patients who were receiving cromolyn sodium was estimated to be 1.27 times (27%) greater than for those who were receiving budesonide inhalation suspension. Secondary: Mean times to first asthma exacerbation and first use of additional long-term asthma medication were significantly longer in patients who were receiving budesonide than in patients receiving cromolyn sodium (P<0.001). Mean improvement in nighttime and daytime asthma symptom scores from baseline to study end were greater in the budesonide group compared to the cromolyn sodium group (P<0.001). Patients in the budesonide group were associated with a significantly decreased utilization of rescue medication from baseline compared with the cromolyn sodium group (P<0.001). Patients treated with budesonide were significantly less likely to have an urgent care visit compared to the cromolyn sodium group (P=0.02). Patients in the budesonide group were associated with a significantly lower rate and duration of oral corticosteroid utilization compared to the cromolyn sodium group (P<0.01). Patients randomized to budesonide exhibited a smaller increase in height

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				from baseline compared to the cromolyn group (P<0.001).
Murphy et al.[7] (2003) Cromolyn sodium 20 mg QID via nebulization for 8 weeks, followed by dose titration vs budesonide 0.5 mg/day via nebulization for 8 weeks, followed by dose titration	MC, OL, PG, RCT Children 2 to 6 years of age with persistent asthma treated with at least one long-term control medication, but no long-term or intermittent oral corticosteroids within 12 weeks and 15 days, respectively, of study entry	N=335 52 weeks	Primary: Impact of a child's asthma on the caregiver's quality of life (PACQLQ), caregiver satisfaction, treatment convenience, ease of use, compliance, child health status (FS-II and CHQ-PF50) Secondary: Not reported	Primary: Improvements in activities and emotional function as well as total PACQLQ scores were significantly greater for caregivers of patients in the budesonide group than in the cromolyn sodium group at all study time points (P<0.05). Mean scores for caregiver satisfaction, convenience, ease of use, and compliance were significantly greater for caregivers of children receiving budesonide, compared to the cromolyn group (P<0.001). Child health status improved from baseline in both study groups as evident by improvements in both FS-II and CHQ-PF50. There was no statistically significant difference between the groups in either questionnaire (P=0.635). Secondary: Not reported
Hoshino et al.[8] (1998) Disodium cromoglycate* (DSCG) 2 mg QID vs ketotifen 1 mg tablet BID vs beclomethasone 100 µg† QID	PG, RCT Patients with mild-moderate atopic asthma, no anti-inflammatory drugs within 4 months of study onset, and no respiratory tract infection within 2 weeks of study entry	N=32 12 weeks	Primary: Symptom score, FEV_1, PEF, bronchial responsiveness, eosinophil count, mast-cell count, CD3, CD4 Secondary: Not reported	Primary: Both DSCG and beclomethasone groups exhibited significant improvement in symptom score compared to the ketotifen group (P<0.05). PEF significantly increased in the DSCG group compared to the ketotifen (P<0.01) and beclomethasone group (P<0.05). FEV_1 increased significantly in the DSCG (P<0.01) and beclomethasone (P<0.05) groups, in comparison to the ketotifen group. Compared with baseline, activated eosinophils, CD3, and CD4 counts were significantly decreased in all three treatment groups (P<0.01). Mast-cell count significantly decreased in the DSCG and beclomethasone groups (P<0.05), but not in the ketotifen group. Secondary: Not reported
Furusho et al.[9]	MC, OL, PRO,	N=257	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Sodium cromoglycate* 1% BID via nebulization vs albuterol 0.5 to 1 mg BID via nebulizer vs albuterol 0.5 to 1 mg and sodium cromoglycate* 1% administered BID via nebulizer	RCT, XO Patients <20 years of age with moderate-severe, allergic or non-allergic perennial asthma, not on maintenance treatment with cromolyn, albuterol, or injected steroids	12 weeks	Change in asthma severity, measured by the mean asthma score Secondary: Patients' opinion of treatment effectiveness	The mean difference in the asthma score reduction was significantly greater in the combination compared to the individual treatments. The mean difference between the combination and albuterol was 7.5 (P<0.001). The mean difference between the combination and sodium cromoglycate was 8.5 (P<0.001). Secondary: Patients preferred combination therapy to treatment with either albuterol (P<0.001) or sodium cromoglycate alone (P<0.01).
Exercise-Induced Bronchospasm				
Kelly et al.[10] (2001) Sodium cromoglycate* (SCG) 4 to 10 mg/day vs nedocromil sodium† 4 to 8 mg/day	MA (8 trials) Patients ≥6 years of age with EIB, with a fall in FEV_1 of >10% after an exercise challenge test	N=117 Variable duration	Primary: Pulmonary function Secondary: Complete protection from exercise-induced broncho-constriction, clinical protection, adverse events	Primary: There was no significant difference between SCG and nedocromil sodium with respect to the maximum percent decrease in FEV_1 analysis (95% CI, 4.49 to 2.74). Secondary: There was no significant difference between SCG and nedocromil sodium with respect to complete protection from EIB (OR, 0.95; 95% CI, 0.50 to 1.81). There was no significant difference between SCG and nedocromil sodium with respect to clinical protection from EIB (OR, 0.71; 95% CI 0.36 to 1.39). There was no significant difference between SCG and nedocromil sodium with respect to unpleasant taste (OR, 6.85; 95% CI, 0.77 to 60.73) or sore

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				throat (OR, 3.46; 95% CI, 0.32 to 37.48).
Spooner et al.[11] (2003) Inhaled mast-cell stabilizers (cromolyn sodium or nedocromil sodium) vs short-acting β_2-agonist, anticholinergic agent, or short-acting β_2-adrenergic agonist in addition to inhaled mast-cell stabilizers	MA (24 trials) Patients $\geq$6 years of age with EIB with a fall in FEV_1 of $\geq$10% after an exercise challenge test	N=518 Variable duration	Primary: Pulmonary function Secondary: Complete protection from exercise-induced broncho-constriction, clinical protection, adverse events, symptom score or preference measure	Primary: On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 7.1%, compared to a 13.8% fall observed in the anticholinergic group (95% CI, 3.3 to 10.0). On average, the maximum percent decrease in FEV_1 after a single dose of either mast-cell stabilizer was 11.2%, compared to a 4.3% fall observed in the β_2-adrenergic agonist group (95% CI, 4.5 to 9.2). Secondary: Mast cell stabilizers provided a greater number of patients with complete protection (73 vs 56%; 95% CI, 1.3 to 3.7) and clinical protection from EIB, compared with anticholinergic agents (73 vs 52%; 95% CI, 1.1 to 6.4). Mast cell stabilizers provided a fewer number of patients with complete protection (66 vs 85%; 95% CI, 0.2 to 0.5) and clinical protection from EIB, compared with β_2-adrenergic agonists (55 vs 77%; 95% CI, 0.2 to 0.8). Patients receiving a combination of a short-acting β_2-adrenergic agonist and a mast-cell stabilizer did not exhibit statistically significant difference in improvement of pulmonary function compared to patients on short-acting β_2-adrenergic agonist alone (5.3 and 3.5% fall, respectively; 95% CI, 0.2 to 1.4).

*Synonym for cromolyn.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QID=four times daily
Study design abbreviations: MA=meta-analysis, MC=multi-center, OL=open-label, PG=parallel-group, PRO=prospective, RCT=randomized trial, XO=crossover
Miscellaneous abbreviations: CHQ-PF50=Modified Child Health Questionnaire-Parent Form 50, CI=confidence interval, EIB=exercise-induced bronchoconstriction, FEV_1=forced expiratory volume in 1 second, FS-II=Functional Status II Questioner, OR=odds ratio, PACQLQ=pediatric asthma caregiver's quality of life questionnaire, PEF=peak expiratory flow

Additional Evidence

Dose Simplification
Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients. Maximum potential adherence was found to be 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn.[12] Murphy et al. evaluated the differences in caregiver satisfaction and adherence to therapy with budesonide inhalation suspension administered once-daily and cromolyn sodium inhalation solution administered four-times-daily. Adherence rates were 76% in the budesonide group compared to 57% in the cromolyn group. Additionally, 54.6% of caregivers rated budesonide as "highly or very convenient" compared with only 23% for cromolyn. While 77% of caregivers found the budesonide formulation easy to administer, only 47% reported ease of use with the cromolyn inhalation. The results of the survey indicated significantly higher parental satisfaction and improved compliance with budesonide compared to cromolyn due to ease of use and convenience of once-daily administration ($P \leq 0.001$).[7]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 8. Relative Cost of the Inhaled Mast-Cell Stabilizers

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cromolyn sodium	inhalation solution*	N/A	N/A	$$$$

*Generic is available in at least one dosage form or strength.
N/A=not available.

X. Conclusions

Cromolyn sodium inhalation solution is the only inhaled mast-cell stabilizer that is currently available in this class. It is approved for the maintenance treatment of asthma, as well as for the prophylaxis of acute bronchospasm induced by exercise, exposure to cold air, or other environmental agents.[1-3] Cromolyn sodium is available in a generic formulation.

Inhaled mast-cell stabilizers have a favorable safety profile but low efficacy for the treatment of asthma.[4] The 2021 Global Initiative for Asthma guidelines do not recommend inhaled mast cell stabilizers for routine use.[4]

Clinical trials have demonstrated that inhaled corticosteroids are more effective than mast-cell stabilizers in patients with persistent asthma.[6-9] Few clinical trials have demonstrated that inhaled mast-cell stabilizers are effective for the prevention of exercise-induced bronchospasm as they are not as effective as short-acting bronchodilators.[10-12]

Therefore, all brand inhaled mast-cell stabilizers within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand inhaled mast-cell stabilizer is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Respiratory Agents-Corticosteroids
AHFS Class 481008
August 10, 2022

I. Overview

The respiratory agents-corticosteroids (inhaled corticosteroids) are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-21] They control airway inflammation by suppressing the migration of leukocytes and fibroblasts, reverse capillary permeability, and prevent phospholipid release at the cellular level. The inhaled corticosteroids are considered the most effective long-term control medication for the treatment of asthma. Most of the clinical benefit from inhaled corticosteroids is seen at low doses, and clear evidence of disease-response relationships is seldom available within the dose ranges evaluated.[22-27]

All of the inhaled corticosteroids are structurally related to endogenously produced corticosteroids, but differ in their mineralocorticoid and glucocorticoid activity. They also differ with regards to their potency, bioavailability, formulation, and dosing schedules. The inhaled corticosteroids are available as single entity products, as well as in combination with a long-acting β_2-agonist (formoterol, salmeterol, or vilanterol). Inhaled β_2-agonists dilate the airways by relaxing bronchial smooth muscle.

Fluticasone furoate (Arnuity Ellipta®) was approved in 2014 for the maintenance treatment of asthma.[8] Fluticasone furoate and fluticasone propionate are distinct drugs with differing pharmacokinetic and pharmacodynamic properties. Fluticasone furoate has enhanced affinity for the target receptors in both nasal and lung tissues and therefore is approved for use at a lower daily dose as compared with fluticasone propionate.[22] The combination product fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta®) was approved in 2017 for the maintenance treatment of patients with COPD. It is the first once-daily single inhaler triple therapy for the treatment of patients with COPD in the US.[14] In 2020, budesonide, glycopyrrolate,e and formoterol fumarate combination (Breztri®), dosed twice daily, was approved for the maintenance treatment of patients with COPD.[19] Two products with built-in electronic modules which detect, record, and store data on inhaler events for transmission to a mobile app, fluticasone propionate (ArmonAir Digihaler®) and fluticasone propionate and salmeterol (Airduo Digihaler®) were approved in 2020 and 2019, respectively.[20,21]

The respiratory agents-corticosteroids that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Many products are currently available in a generic formulation, including single entity and combination products. This class was last reviewed in May 2020.

Table 1. Respiratory Agents-Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Beclomethasone	aerosol inhaler	QVAR®	QVAR®
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort Flexhaler®, Pulmicort Respules®*	Pulmicort Flexhaler®
Ciclesonide	aerosol inhaler	Alvesco®	none
Fluticasone furoate	dry powder inhaler	Arnuity Ellipta®	Arnuity Ellipta®
Fluticasone propionate	aerosol inhaler, dry powder inhaler	ArmonAir Digihaler®, Flovent Diskus®, Flovent HFA®*	Flovent Diskus®, Flovent HFA®*, fluticasone propionate
Mometasone	aerosol inhaler, dry powder inhaler	Asmanex HFA®, Asmanex Twisthaler®	Asmanex HFA®, Asmanex Twisthaler®
Combination Products			
Budesonide and formoterol	aerosol inhaler	Symbicort®*	budesonide and formoterol, Symbicort®*

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Budesonide, glycopyrrolate, and formoterol	aerosol inhaler	Breztri®	none
Fluticasone propionate and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®*, Advair HFA®, Airduo Digihaler®, Airduo Respiclick®*	Advair Diskus®*, Advair HFA®, Airduo Respiclick®*
Fluticasone furoate and vilanterol	dry powder inhaler	Breo Ellipta®*	Breo Ellipta®*. fluticasone furoate and vilanterol
Fluticasone furoate, umeclidinium, and vilanterol	dry powder inhaler	Trelegy Ellipta®	none
Mometasone and formoterol	aerosol inhaler	Dulera®	Dulera®

*Generic is available in at least one dosage form or strength.
HFA=hydrofluoroalkane, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory agents-corticosteroids are summarized in Table 2.

Table 2. Treatment Guidelines Using the Respiratory Agents-Corticosteroids

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022)**[23]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, sputum production, history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease. • Spirometry is required to make the diagnosis; the presence of a post-bronchodilator Forced Expiratory Volume in one second (FEV_1)/ Forced Vital Capacity (FVC) ratio of <0.07 confirms the presence of persistent airflow limitation. • The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbation, hospital admissions, or death), in order to guide therapy. • Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer; these comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalizations independently. Prevention and maintenance therapy • Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. • The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present. • Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. • Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices. • Inhaler technique needs to be assessed regularly. • COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations.

Clinical Guidelines	Recommendations
	• Influenza vaccination decreases lower respiratory tract infections. • Pneumococcal vaccination decreases lower respiratory tract infections. • CDC recommends the Tdap vaccination (dTaP/dTPa) in COPD patients to protect against pertussis, tetanus and diphtheria, in those who were not vaccinated in adolescence and Zoster vaccine to protect against shingles for adults with COPD aged ≥50 years. • Pulmonary rehabilitation improves exercise capacity, symptoms and quality of life across all grades of COPD severity. • In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival. • In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. Individual patient factors must be considered when evaluating the patient's need for supplemental oxygen. • In patients with severe chronic hypercapnia and a history of hospitalizations for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization. • In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial. • Palliative approached are effective in controlling symptoms in advanced COPD. <u>Pharmacologic therapy for stable COPD</u> • Bronchodilators o Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. o Regular and as-needed use of short-acting β_2-agonist (SABA) or short-acting antimuscarinic (SAMA) improves FEV_1 and symptoms. o Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms. o Long-acting β_2-agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) improve lung function, dyspnea, health status, and reduce exacerbation rates. o LAMAs have a greater effect on reducing exacerbations than LABAs and decrease hospitalizations. o Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy. o Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy. o Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance. o Theophylline exerts a small bronchodilator effect in stable COPD and that is associated with modest symptomatic benefits. • Anti-inflammatory therapy o Inhaled corticosteroids ▪ An inhaled corticosteroid (ICS) combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. ▪ Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease. ▪ Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.

Clinical Guidelines	Recommendations
	○ Oral glucocorticoids ▪ Long-term use of oral glucocorticoids has numerous side effects with no evidence of benefits. ○ Phosphodiesterase-4 (PDE4) inhibitors ▪ In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations, a PDE4 inhibitor improves lung function and reduces moderate to severe exacerbations and improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations. ○ Antibiotics ▪ Long-term azithromycin and erythromycin therapy reduces exacerbations over one year. ▪ Treatment with azithromycin is associated with an increased incidence of bacterial resistance and hearing test impairments. ○ Mucoregulators and antioxidant agents ▪ Regular treatment with mucolytics such as erdosteine, carbocysteine, and N-acetylcysteine (NAC) reduces the risk of exacerbations in select populations. ○ Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy. ○ Leukotriene modifiers have not been adequately tested in COPD patients. ○ Intravenous augmentation therapy may slow down the progression of emphysema. ○ There is no conclusive evidence of a beneficial role of antitussives in patients with COPD. Vasodilators do not improve outcomes and may worsen oxygenation. <u>Management of stable COPD</u> • LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy. • Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. • Inhaled bronchodilators are recommended over oral bronchodilators. • Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable. • Long-term monotherapy with ICS is not recommended. • Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators. • Long-term therapy with oral corticosteroids is not recommended. • In patients with severe to very severe airflow limitation, chronic bronchitis, and exacerbations the addition of a PDE4 inhibitor to a treatment with long-acting bronchodilators with/without ICS can be considered. • Preferentially but not only in former smokers with exacerbations despite appropriate therapy, macrolides (in particular azithromycin) can be considered. • Statin therapy is not recommended for prevention of exacerbations. • Antioxidant mucolytics are recommended only in select patients. • Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. • Antitussives cannot be recommended. • Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD. • Low-dose long acting oral and parenteral opioids may be considered for treating

Clinical Guidelines	Recommendations
	dyspnea in COPD patients with severe disease. Management of exacerbations • The most common causes of an exacerbation are viral respiratory tract infections. • The goal of treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events. • SABA with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation. • Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge. • Systemic corticosteroids can improve lung function (FEV_1), oxygenation, and shorten recovery time and length of hospital stay. Duration of therapy should not be more than five to seven days. • Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be five to seven days. • Methylxanthines are not recommended due to increased side effect profiles.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)[24]**	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted.

Clinical Guidelines	Recommendations
	• Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
Department of Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2021)**[25]	Diagnosis and classification • Post-bronchodilator spirometry is suggested to confirm clinical diagnosis of COPD. • There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD. Risk reduction and first-line therapy • Smoking cessation is recommended for prevention and risk reduction of COPD. • Routine vaccination for influenza and pneumococcal pneumonia is suggested for prevention and risk reduction of COPD exacerbations. • LAMA is recommended as first-line therapy in patients with symptomatic COPD. • Inhaled LABA should not be offered as first-line therapy in patients with symptomatic COPD, unless a LAMA is not tolerated or is contraindicated. • ICS should not be offered to patients with symptomatic COPD as a first-line therapy. • For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a LAMA, adding a LABA to LAMA therapy is suggested. • If choosing dual therapy, offering LABA with ICS for patients with COPD is not recommended. • In patients with COPD who are on combination therapy with a LAMA/LABA and continue to have COPD exacerbations, adding an ICS as a third medication is suggested. • There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy. • Consider withdrawal of ICS in patients with COPD without moderate to severe exacerbations in the last two years. • There is insufficient evidence to recommend for or against the use of NAC preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). • There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not). • Providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia or chronic stable resting moderate hypoxemia with signs of tissue hypoxia is recommended. • Routinely offering ambulatory long-term supplemental oxygen is not suggested for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. • In patients with COPD, starting or continuing cardio-selective beta-blockers is suggested only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction). • Supported self-management program and telehealth support should be offered.
Global Initiative for Asthma: **Global Strategy for Asthma Management and**	General principles of asthma management • The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.

Clinical Guidelines	Recommendations

Prevention (2021)[26]	• Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers.
	• Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.
	• Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences.
	• For population-level decisions about asthma treatment, the 'preferred option' represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	<u>Medications and strategies for symptom control and risk reduction</u>
	• For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone.
	• This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms.
	• Choice of reliever
	  ○ Low dose ICS-formoterol is the preferred approach recommended by this guideline.
	  ○ SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy.
	• Mild asthma
	  ○ Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	  ○ In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control.
	• Stepping up if asthma remains uncontrolled despite good adherence and inhaler technique
	  ○ Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities.
	  ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium.
	  ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age.
	  ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA.
	  ▪ For children, try other controller options at the same step before stepping up.
	  ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking.
	• Stepping down to find the minimum effective dose
	  ○ Consider step down once good asthma control has been achieved and

Clinical Guidelines	Recommendations
	maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. • For all patients with asthma o Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect. o Encourage adherence with controller medication, even when symptoms are infrequent. o Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations. o For patients with one or more risk factors for exacerbations: ▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function). ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies). • Difficult-to-treat and severe asthma o Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics. <u>Categories of asthma medications</u> • *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise. • *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment. • *Add-on therapies for patients with severe asthma*: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. <u>Initial controller treatment</u> • For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made. <u>Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u> • Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or

Clinical Guidelines	Recommendations

down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.

- If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  - Incorrect inhaler technique.
  - Poor adherence.
  - Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  - Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  - Incorrect diagnosis.

Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)					
Controller and preferred reliever (Track 1)	**Steps 1 to 2** As-needed low dose ICS-formoterol		**Step 3** Low dose maintenance ICS-formoterol	**Step 4** Medium dose maintenance ICS-formoterol	**Step 5** Add-on LAMA Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-formoterol
	Reliever: as-needed low-dose ICS-formoterol				
Controller and alternative reliever (Track 2)	**Step 1** Take ICS whenever SABA taken	**Step 2** Low dose maintenance ICS	**Step 3** Low dose maintenance ICS-LABA	**Step 4** Medium/high dose maintenance ICS-LABA	**Step 5** Add-on LAMA Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R Consider high dose ICS-LABA
	Reliever: as-needed SABA				

- Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS

Personalized management to control symptoms and minimize future risk (six to 11 years of age)					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Preferred controller	Low dose ICS taken when SABA is taken	Daily low dose ICS	Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy	Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)
Other controller options	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken	Low dose ICS+LTRA	Add tiotropium, or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side effects
Reliever	As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)				

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung

Clinical Guidelines	Recommendations
	function from the patient's usual status, or in some cases, the initial presentation of asthma. • Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review. • All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma. o The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment. o Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately. o The action plan can be based on changes in symptoms or (in adults) peak expiratory flow. • For patients presenting with an exacerbation to a primary care or acute care facility: o Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy. o Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given. o Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be reviewed after one hour. o Ipratropium bromide treatment is recommended only for severe exacerbations. o Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment. o Chest X-ray or prescribing antibiotics is not routinely recommended. o Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home. o Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use. • Arrange early follow-up after any exacerbation, regardless of where it was managed. o Review the patient's symptom control and risk factors for further exacerbations. o Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks. o Provide a written asthma action plan and advice about avoiding exacerbation triggers. o Check inhaler technique and adherence. <u>Children five years and younger: assessment and management</u> • The goals of asthma management in young children are similar to those in older patients: o To achieve good control of symptoms and maintain normal activity levels. o To minimize the risk of asthma flare-ups, impaired lung development, and

Clinical Guidelines	Recommendations

medication side effects.

- Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective.
- A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Personalized management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

Management of worsening asthma and exacerbations in children five and younger

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.
- Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required.
  - Initial treatment at home is with inhaled SABA, with review after one hour or earlier.
  - Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age.
  - Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours.
  - There is no compelling evidence to support parent-initiated oral corticosteroids.
- In children presenting to primary care or an acute care facility with an asthma exacerbation:
  - Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain

Clinical Guidelines	Recommendations
	saturation 94 to 98%). ○ Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air. ○ Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days for children attending an emergency department or admitted to hospital, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma management.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2019)**[27]	<u>Pharmacological management</u> • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%. • Intermittent reliever therapy: ○ For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. ○ For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. ○ Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: ○ ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five years of age with asthma. ○ ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. ○ ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. ○ ICS should initially be administered twice daily, except ciclesonide which is administered once daily. ○ Once a day ICS at the same total daily dose can be considered if good control is established. ○ Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: ○ In adults, the first choice add-on therapy to an ICS is a LABA, which should

Clinical Guidelines	Recommendations
	be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. o In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: o If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: o All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. o If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed) ▪ Add tiotropium (adults) ▪ Add a theophylline. o If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). o Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored. o Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. o Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. o The use of immunotherapy is not recommended for the treatment of asthma in adults or children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory agents-corticosteroids are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity Respiratory Agents-Corticosteroids[1-21]

Indication	Beclomethasone	Budesonide	Ciclesonide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Asthma						
Maintenance treatment of asthma as prophylactic therapy in children 12 months to 8 years of age		✔ (Inhalation suspension)				
Maintenance treatment of asthma as prophylactic therapy in patients ≥4 years of age					✔ (Flovent®)	✔ (DPI)
Maintenance treatment of asthma as prophylactic therapy in patients ≥5 years of age	✔			✔		✔ (MDI)
Maintenance treatment of asthma as prophylactic therapy in patients ≥6 years of age		✔ (DPI)				
Maintenance treatment of asthma as prophylactic therapy in patients ≥12 years of age			✔		✔ (ArmonAir Digihaler®)	

DPI=Dry powder inhaler, MDI=metered dose inhaler

Table 4. FDA-Approved Indications for the Combination Respiratory Agents-Corticosteroids[1-21]

Indication	Budesonide and Formoterol	Budesonide, glycopyrrolate and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Fluticasone furoate, umeclidinium, and vilanterol	Mometasone and Formoterol
Asthma						
Maintenance treatment of asthma in patients 18 years of age and older					✔	
Treatment of asthma in patients 4 years of age and older			✔ (Advair Diskus®)			
Treatment of asthma in patients 5 years of age and older						✔
Treatment of asthma in patients 6 years of age and older	✔					
Treatment of asthma in patients 12 years of age and older			✔ (Advair HFA®, Airduo Respiclick® and Airduo Digihaler®)			
Treatment of asthma in patients aged ≥18 years				✔		
COPD						
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema	✔ (Symbicort®		✔ (Advair	✔ (Breo		

Indication	Budesonide and Formoterol	Budesonide, glycopyrrolate and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Fluticasone furoate, umeclidinium, and vilanterol	Mometasone and Formoterol
	160/4.5 µg)		Diskus® 250/50 µg)	Ellipta® 100/25µg)		
Maintenance treatment of patients with COPD		✔			✔ (Trelegy Ellipta® 100/62.5/25 µg)	
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (Symbicort® 160/4.5 µg)		✔ (Advair Diskus® 250/50 µg)	✔ (Breo Ellipta® 100/25 µg)		

COPD=chronic obstructive pulmonary disease.

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory agents-corticosteroids are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Respiratory Agents-Corticosteroids[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Beclomethasone	Not available	94 to 96	Hepatic and respiratory	Renal (<10) Feces (main, percent not specified)	2.8
Budesonide	39	85 to 90	Hepatic extensive	Renal (60) Feces (15.1 to 29.6)	2.0 to 3.6
Ciclesonide	<1	≥99	Hepatic predominantly, respiratory	Renal (<20) Feces (66)	6 to 7
Fluticasone furoate	13.9	>99	Hepatic, extensive	Renal (1) Feces (100)	24
Fluticasone propionate	<1	99	Hepatic	Renal (<5) Feces (95)	7.8 to 11.2
Mometasone	<1	98 to 99	Hepatic, extensive	Renal (8) Feces (74)	5.0 to 5.8
Combination Products					
Budesonide and formoterol	B: 39 F: Not reported	B: 85 to 90 F: 31 to 64	Hepatic extensive	B: Renal (60) Feces (15.1 to 29.6) F: Renal (59 to 62) Feces (32 to 34)	B: 2.0 to 3.6 F: 7 to 10
Budesonide, glycopyrrolate and formoterol	B: Not reported G: Not reported F: Not reported	B: 86 to 87 G: 43 to 54 F: 46 to 58	B: Hepatic extensive G: Hepatic, minor F: Heaptic, extensive	B: Not reported G: Renal (85) F: Renal (62) Feces (24)	B: 5 G: 15 F: 10
Fluticasone propionate and salmeterol	F: <1 S: Not reported	F: 99 S: 96	Hepatic	F: Renal (<5) Feces (95) S: Renal (25) Feces (60)	F: 5.6 to 11.2 S: 5.5 to 12.6
Fluticasone furoate and vilanterol	F: 15.3 V: 27.3	F: >99 V: >93	F: Hepatic, extensive V: Hepatic, unknown	F: Renal (1) Feces (100) V: Renal (70) Feces (30)	F: 24 V: 16 to 21.3
Fluticasone furoate, umeclidinium, and vilanterol	F: 15.2 U: Not reported V: Not reported	F: >99 U: 89 V: 94	F: Hepatic, extensive U: Hepatic, extensive V: Hepatic, extensive	F: Renal (1) Feces (100) U: Renal (1) Feces (92) V: Renal (70) Feces (30)	F: 24 U: 11 V: 11
Mometasone and formoterol	M: <1 F: Not reported	M: 98 to 99 F: 31 to 64	Hepatic, extensive	M: Renal (8) Feces (74) F: Renal (59 to 62) Feces (32 to 34)	M:5.0 to 5.8 F: 7 to 10

V. Drug Interactions

Significant drug interactions with the respiratory agents-corticosteroids are listed in Table 6.

Table 6. Significant Drug Interactions with the Respiratory Agents-Corticosteroids[1-21]

Generic Name(s)	Interaction	Mechanism
Budesonide, fluticasone	Human immunodeficiency virus (HIV) protease Inhibitors	Plasma concentrations and pharmacologic effects of specific inhaled steroids may be increased by HIV protease inhibitors. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur. Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of specific inhaled steroids. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
Formoterol, salmeterol, vilanterol	Beta-adrenergic blockers	Pharmacologic effects of inhaled beta agonists may be decreased by beta-adrenergic blockers. Untoward physiologic effects, characterized by bronchospasm, may occur. Non-cardioselective beta-adrenergic blockers may block the bronchodilating effects of inhaled beta agonists.
Formoterol, salmeterol, vilanterol	Monoamine oxidase inhibitors (MAOI's) and tricyclic antidepressants (TCAs)	Concurrent administration of inhaled beta agonists with MAOIs or TCAs may potentiate the adrenergic effects on the cardiovascular system caused by the inhaled beta agonists.
Formoterol, salmeterol, vilanterol	Non–Potassium-Sparing Diuretics	The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics can be acutely worsened by beta agonists.
Budesonide, fluticasone	Azole antifungals	Azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids (budesonide and fluticasone only) resulting in enhanced corticosteroid effects and toxicity.
Budesonide	Anticoagulants	Both an increase in the dosage requirement of anticoagulants and hemorrhagic episodes have been reported with this combination.
Budesonide	Barbiturates	Pharmacologic effects of budesonide may be decreased with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by barbiturates may increase the metabolic elimination of budesonide.
Budesonide	Hydantoins	Pharmacologic effects of budesonide may be decreased, with possible exacerbation of the disease being treated. Plasma concentrations and therapeutic effects of hydantoins may be decreased by budesonide. Induction of hepatic microsomal enzymes by hydantoins may increase the metabolic elimination of budesonide.
Budesonide	Mifepristone	The pharmacologic effects of budesonide may be reduced. Mifepristone antagonizes the pharmacologic effects of budesonide. Coadministration of budesonide with mifepristone is contraindicated.
Budesonide	Rifamycins	Pharmacologic effects of budesonide may be decreased by rifamycins with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of budesonide. Induction of hepatic

Generic Name(s)	Interaction	Mechanism
		microsomal enzymes by rifamycins may increase the metabolic elimination of budesonide.
Glycopyrrolate	Potassium	Concurrent use of glycopyrrolate and potassium may result in risk of gastrointestinal lesions.
Glycopyrrolate	Anticholinergics	Concurrent use of glycopyrrolate and anticholinergics may result in increased risk of anticholinergic side effects.
Umeclidinium	Anticholinergics	Concurrent use of inhaled antimuscarinics and anticholinergics may result in increased risk of anticholinergic side effects.
Umeclidinium	Bupropion	Concurrent use of bupropion and inhaled antimuscarinics may result in lower seizure threshold.
Umeclidinium	Donepezil	Concurrent use of donepezil and inhaled antimuscarinics may result in reduced seizure threshold.

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory agents-corticosteroids are listed in Tables 7 to 8. The boxed warnings have been removed from the combination products in this class, and warnings were added for serious asthma-related events. The warning states that use of long-acting β_2-agonists (LABAs) as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABAs are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.[1-21]

Table 7. Adverse Drug Events (%) Reported with the Single Entity Respiratory Agents-Corticosteroids[1-21]

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Cardiovascular						
Chest pain	-	1 to 3†	<1	-	✔ §; 1 to 3†	-
Palpitations	-	-	<1	-	-	-
Syncope	-	1 to 3§	-	-	-	-
Central Nervous System						
Anxiety	-	-	-	-	✔ §†	-
Depression	-	-	-	-	✔ §†	-
Dizziness	-	-	≥3	-	✔ §; 1 to 3†	-
Emotional lability	-	1 to 3†	-	-	✔ §†	-
Headache	12 to 15	13 to 14§	4.9 to 11	6 to 13	2 to 14§; 5 to 11†, 1.6 to 7.3‡	17 to 22
Hyperkinesia	-	1 to 3†	-	-	✔ §†	-
Hypertonia	-	1 to 3§	-	-	-	-
Insomnia	-	1 to 3§	-	-	-	1 to 3
Migraine	-	1 to 3§	-	-	✔ §; 1 to 3†	-
Dermatological						
Angioedema	-	-	-	-	✔ §†	-
Ecchymosis	-	1 to 3§	<1	-	✔ §†	-
Eczema	-	1 to3†	-	-	-	-
Pruritus	-	1 to 3†	-	-	✔ §†	-
Purpura	-	1 to 3†	-	-	-	-
Pustular rash	-	1 to 3†	-	-	-	-
Rash	-	1 to 4†	<1	-	-	-
Skin infection	-	-	-	-	✔ §; 1 to3†	-
Vasculitis	-	-	-	-	✔ §†	-
Endocrine and Metabolic						

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Cushingoid features	-	-	-	-	✔ §†	-
Edema	-	-	-	-	✔ §†	-
Hyperglycemia	-	-	-	-	✔ §†	-
Osteoporosis	-	-	-	-	✔ §†	-
Gastrointestinal						
Anorexia	-	1 to 3†	-	-	-	1 to 3
Diarrhea	-	2 to 4†	-	-	✔ §; 1 to 3†	-
Dry mouth	-	1 to 3§	<1	-	-	-
Dyspepsia	-	1 to 4§	<1	-	✔ §; 1 to 3†	3 to 5
Flatulence	-	-	-	-	-	1 to 3
Gastroenteritis	-	1 to 3§; 4 to 5†	≥3	3	-	1 to 3
Gastrointestinal pain	-	1 to 3§; 2 to 3†	-	0 to 3	✔ §; 1 to 3†	2 to 3
Nausea	1 to 3	1 to 3§	<1	-	-	1 to 3
Oral candidiasis	-	2 to 4§	≥3	<1 to 3	1 to 9§; 2 to 5†, 2.9 to 4.8‡	4 to 6
Taste alteration	-	1 to 3§	-	-	-	-
Vomiting	-	2 to 4†	-	-	-	1 to 3
Genitourinary						
Dysuria	-	-	-	-	<1§†	-
Polyuria	-	-	-	-	✔ §; <3†	-
Urinary tract infection	-	-	-	-	-	1 to 3
Hematologic						
Enlarged lymph nodes	-	-	-	-	-	-
Musculoskeletal						
Arthralgia	-	-	≤4	≥3	-	-
Fracture	-	1 to 3§†	-	-	-	-
Myalgia	-	1 to 3§†	-	-	2 to 3	-
Respiratory						
Bronchitis	-	-	-	7 to 12	0 to 8§; 2 to 6†	-
Coughing	1 to 3	5 to 8†	<1	0 to 3	1 to 5§; 4 to 6†, 1.6 to 3.4‡	-
Dyspnea	-	✔ †	-	-	✔ §†	-
Hoarseness	-	-	-	-	✔ §; 2 to 6†	-
Increased asthma symptoms	3 to 8	-	-	-	✔ §†	-
Nasal congestion	-	-	2 to 6	≥3	-	-
Nasopharyngitis				8 to 13	4.8 to 5.8‡	-

Adverse Events	Beclomethasone	Budesonide	Ciclesonide	Fluticasone Furoate	Fluticasone Propionate	Mometasone
Pharyngitis	8 to 10	5 to 10§	7 to 11	3 to 6	✔ §†	11 to 13
Pneumonia	-	-	≥3	-	-	-
Rhinitis	6 to 11	7 to 12†	-	<1 to 3	✔ §†	11 to 15
Rhinorrhea	-	-	<1	-	-	-
Sinusitis	-	2 to 11§	≤6	4 to 7	6 to 10§; 4 to 7†	-
Stridor	-	1 to 3†	3 to 5	-	-	-
Throat irritation	-	-	<1	<1 to 3	-	-
Upper respiratory tract infection	9 to 12	19 to 24§; 34 to 38†	4 to 7	2 to 6	14 to 20§; 16 to 18†, 4.7 to 5.5‡	8 to 15
Wheezing	-	✔ †	-	-	✔ §†	-
Other						
Back pain	1 to 4	2 to 6§	1 to 3	3	-	3 to 6
Conjunctivitis	-	1 to 2†	≥3	-	-	-
Dysmenorrhea	1 to 3	-	-	-	-	4 to 9
Dysphonia	2 to 4	1 to 6§; 1 to 3†	<1	2 to 3	-	1 to 3
Ear pain	-	1 to 3†	≤2	-	-	1 to 3
Ear infection	-	2 to 5†	-	-	-	-
Epistaxis	-	2 to 4†	-	-	-	1 to 3
Eye infection	-	1 to 3†	-	-	-	-
Fever	-	2 to 4§	-	-	1 to 7§; 1 to 3†	-
Flu syndrome	-	6 to 14§; 1 to 3†	-	4 to 7	-	-
Hypersensitivity reaction	-	1 to 3†	-	-	-	-
Infection	-	1 to 3§†	-	-	-	1 to 3
Intraocular pressure increased	-	-	<1	-	-	-
Moniliasis	-	3 to 4†	-	-	-	-
Neck pain	-	1 to 3§	-	-	-	-
Otitis media	-	9 to 12†	-	-	-	-
Pain	2 to 3	5§	0 to 3	-	✔ §; 1 to 3†	1 to 3
Throat Pain	-	-	2 to 5	3 to 4	✔ §†	-
Toothache	-	-	-	<1 to 3	-	-
Viral infection	-	3 to 5†	-	-	-	-
Weight gain	-	1 to 3§	<1	-	✔ §†	-

✔ Percent not specified.
- Event not reported.
§ Flovent Diskus®
† Flovent HFA®
‡ArmonAir Digihaler®

Table 8. Adverse Drug Events (%) Reported with the Combination Respiratory Agents-Corticosteroids[1-21]

Adverse Event	Budesonide and Formoterol	Budesonide, Glycopyrrolate and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Fluticasone, Umeclidinium, and Vilanterol	Mometasone and Formoterol
Ear, Nose, and Throat						
Candidiasis, oral	1.4 to 3.2	3.0	1 to 4	5	≥1	-
Hoarseness/dysphonia	<3	-	2 to 5	-	-	-
Nasal congestion	2.5 to 3.2	-	-	-	-	-
Nasopharyngitis	9.7 to 10.5	-	4.8 to 8.6	9	-	4.7
Pharyngitis	<3	-	10 to 13	≥3	≥1	-
Pharyngolaryngeal pain	6.1 to 8.9	-	-	≥3	1	-
Sinusitis	4.8 to 5.8	2.6	4 to 5	≥3	≥1	2.0 to 3.3
Upper respiratory infection	7.6 to 10.5	5.7	21 to 27	7	≥1	-
Upper respiratory inflammation	-	-	6 to 7	-	-	-
Lower Respiratory						
Bronchitis	<4	-	2 to 8	≥3	≥1	-
Cough	<4	2.7	0.7 to 6	≥3	1	-
Pneumonia	-	4.6	-	6	8	-
Viral respiratory infections	-	-	4	-	-	-
Neurology						
Headache	6.5 to 11.3	-	2.8 to 21	7	4	2.0 to 4.5
Gastrointestinal						
Constipation	-	-	-	-	≥1	-
Gastrointestinal discomfort	1.1 to 6.5	-	1 to 4	-	-	-
Diarrhea	-	2.1	2 to 4	≥3	2	-
Gastroenteritis	-	-	-	-	1	-
Influenza	2.4 to 3.2	2.9	-	≥3	≥1	-
Nausea/vomiting	1.4 to 3.2	-	4 to 6	-	-	-
Viral gastrointestinal infections	-	-	<3	-	-	-
Other						
Arthralgia	-	-	-	≥3	≥1	-
Back pain	1.6 to 3.2	3.1	0 to 3.1	≥3	4	-
Candidiasis, unspecified site	-	-	<3	-	-	-
Fever	-	-	-	≥3	-	-
Hypertension	-	-	-	≥3	-	-
Muscle spasm	-	2.8	-	-	-	-
Musculoskeletal pain	-	-	2 to 7	-	-	-

Adverse Event	Budesonide and Formoterol	Budesonide, Glycopyrrolate and Formoterol	Fluticasone Propionate and Salmeterol	Fluticasone Furoate and Vilanterol	Fluticasone, Umeclidinium, and Vilanterol	Mometasone and Formoterol
Peripheral edema	-	-	-	≥3	-	-
Urinary tract infection	-	2.7	-	-	≥1	-

- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the respiratory agents-corticosteroids are listed in Table 9. The estimated comparative daily doses for the available products are listed in Table 10.

Table 9. Usual Dosing Regimens for the Respiratory Agents-Corticosteroids[1-21]

Generic Name(s)	Usual Adult/Adolescent Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Beclomethasone	Asthma: Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators: initial, 40 to 80 µg BID; maximum, 320 µg BID; patients treated previously with an inhaled corticosteroid; initial, 40 to 320 µg BID; maximum, 320 µg BID	Asthma: Meter dose aerosol inhaler (HFA): 5 to 11 years of age: initial, 40 µg BID; maximum, 80 µg BID	Meter dose aerosol inhaler (HFA): 40 µg 80 µg
Budesonide	Asthma: Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID	Asthma: Dry powder inhaler: children six to 17 years of age; initial, 180 µg BID (selected patients can be initiated at 360 µg BID); maximum, 360 µg BID Suspension for nebulization: children 12 months to eight years of age treated previously with only bronchodilators; initial, 0.5 mg total daily dose administered either QD or in divided doses; maximum, 0.5 mg total daily dose; children 12 months to eight years of age treated previously with an inhaled corticosteroid; initial, 0.5 mg total daily dose administered either QD or BID in divided doses; maximum, 1 mg total daily dose; children 12 months to eight years of age treated previously with an oral corticosteroid; initial, 1 mg total daily dose administered either as 0.5 mg BID or 1 mg QD; maximum, 1 mg total daily dose	Dry powder inhaler: 90 µg 180 µg Suspension for nebulization: 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL
Ciclesonide	Asthma: Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 80 µg BID; maximum, 160 µg BID; patients treated previously with	Not indicated for children <12 years of age.	Meter dose aerosol inhaler (HFA): 80 µg 160 µg

Generic Name(s)	Usual Adult/Adolescent Dose	Usual Pediatric Dose	Availability
	an inhaled corticosteroid; initial, 80 µg BID; maximum, 320 µg BID; patients treated previously with oral corticosteroids; initial, 320 µg BID; maximum, 320 µg BID		
Fluticasone furoate	Asthma: Dry powder inhaler: 1 inhalation once daily, beginning with 100 or 200 µg based on previous therapy; maximum, 200 µg daily	Asthma: Dry powder inhaler: children five to 11 years of age; 50 µg once daily	Dry powder inhaler: 50 µg 100 µg 200 µg
Fluticasone propionate	Asthma: Dry powder inhaler (Flovent Diskus®): starting dosage is based on prior asthma therapy and disease severity; initial, 100 µg BID; maximum, 1,000 µg BID Dry powder inhaler (ArmonAir Digihaler®): starting dosage is based on prior asthma therapy and disease severity; 1 inhalation (55 µg, 113 µg, 232 µg) twice daily Meter dose aerosol inhaler (HFA): starting dosage is based on prior asthma therapy and disease severity; initial, 88 µg BID; maximum, 880 µg BID	Asthma: Dry powder inhaler (Flovent Diskus®): children four to 11 years of age; starting dosage is based on prior asthma therapy and disease severity; initial, 50 µg BID; maximum, 100 µg BID Dry powder inhaler (ArmonAir Digihaler®): children ≥12 years of age; starting dosage is based on prior asthma therapy and disease severity; 1 inhalation (55 µg, 113 µg, 232 µg) twice daily Meter dose aerosol inhaler (HFA): children four to 11 years of age; initial 88 µg BID; maximum, 88 µg BID	Dry powder inhaler (Flovent Diskus®): 50 µg 100 µg 250 µg Dry powder inhaler (ArmonAir Digihaler®): 55 µg 113 µg 232 µg Meter dose aerosol inhaler (Flovent HFA®): 44 µg 110 µg 220 µg
Mometasone	Asthma: Dry powder inhaler: patients treated previously with only bronchodilators or inhaled corticosteroids; initial, 220 µg QD in the evening; maximum, 440 µg administered as QD in the evening or as 220 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg daily Meter dose aerosol inhaler (HFA): patients treated previously with inhaled medium-dose corticosteroids; initial, 100 µg 2 inhalations BID; patients treated previously with high-dose oral corticosteroids; initial, 200 µg 2 inhalations BID; maximum, 2 inhalations of 200 µg BID	Asthma: Dry powder inhaler: children four to 11 years of age; initial, 110 µg QD in the evening; maximum, 110 µg QD in the evening Meter dose aerosol inhaler (HFA): children five to 11 years of age; two inhalations of 50 µg BID	Dry powder inhaler (Twisthaler®): 110 µg 220 µg Meter dose aerosol inhaler (HFA): 100 µg 200 µg

Generic Name(s)	Usual Adult/Adolescent Dose	Usual Pediatric Dose	Availability
Combination Products			
Budesonide and formoterol	Asthma: Meter dose aerosol inhaler (HFA): initial, two inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, for patients who do not respond adequately to the starting dose after one to two weeks with 80-4.5 µg, consideration to using 160-4.5 µg can be made to provide additional asthma control; maximum, 160-4.5 µg BID COPD*†: Meter dose aerosol inhaler (HFA): 160/4.5 µg, two inhalations BID	Asthma: Meter dose aerosol inhaler (HFA): children six to 11 years of age; initial, 80/4.5 µg two inhalations BID; maximum, 80/4.5 µg two inhalations BID Safety and efficacy of meter dose aerosol inhaler (HFA) in children <6 years of age have not been established.	Meter dose aerosol inhaler (HFA): 80-4.5 µg 160-4.5 µg
Budesonide, glycopyrrolate and formoterol	COPD: Meter dose aerosol inhaler (HFA): two 160/9/4.8 µg inhalations BID	Safety and efficacy in children <18 years of age have not been established.	Meter dose aerosol inhaler (HFA): 160-9-4.8 µg
Fluticasone propionate and salmeterol	Asthma: Dry powder inhaler (Advair Diskus®): initial, one inhalation BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 500-50 µg BID Dry powder inhaler (Airduo Respiclick®): initial, one inhalation BID, for patients not on an inhaled corticosteroid, 55/14 µg BID, for other patients the dose should be based on previous asthma treatment and severity; maintenance, for patients who do not respond after two weeks of therapy, increasing the dose may provide additional asthma control; maximum, 232-14 µg BID Meter dose aerosol inhaler (Advair HFA®): initial, two	Asthma: Dry powder inhaler (Advair Diskus®): children 4 to 11 years of age who are not controlled on an inhaled corticosteroid; 100-50 µg one inhalation BID Dry powder inhaler (Airduo Digihaler®): children ≥12 years of age; starting dosage is based on prior asthma therapy and disease severity; 1 inhalation (55-14 µg, 113-14 µg, 232-14 µg) twice daily Safety and efficacy in children <4 years of age have not been established for the dry powder inhaler (Advair Diskus®). Safety and efficacy in children <12 years of age have not been established for the dry powder inhaler (Airduo Respiclick® and Airduo Digihaler®), the meter dose aerosol inhaler (Advair HFA®).	Dry powder inhaler (Advair Diskus®): 100-50 µg 250-50 µg 500-50 µg Dry powder inhaler (Airduo Respiclick®): 55-14 µg 113-14 µg 232-14 µg Dry powder inhaler (Airduo Digihaler®): 55 µg-14 µg 113 µg-14 µg 232 µg-14 µg Meter dose aerosol inhaler (Advair HFA®): 45-21 µg 115-21 µg 230-21 µg

Generic Name(s)	Usual Adult/Adolescent Dose	Usual Pediatric Dose	Availability
	inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 230-21 µg two inhalations BID Multidose dry powder inhaler (Airduo Digihaler®): Starting dosage is based on prior asthma therapy and disease severity; 1 inhalation (55-14 µg, 113-14 µg, 232-14 µg) twice daily COPD*‡: Dry powder inhaler (Advair Diskus®): 250-50 µg one inhalation BID		
Fluticasone furoate and vilanterol	Asthma: Dry powder inhaler: one 100-25 µg or 200-25 µg inhalation once daily; maximum, 200-25 µg inhalation once daily COPD*: Dry powder inhaler: one 100-25 µg inhalation once daily	Safety and efficacy in children <18 years of age have not been established.	Dry powder inhaler: 100-25 µg 200-25 µg
Fluticasone furoate, umeclidinium, and vilanterol	Asthma: Dry powder inhaler: one 100-62.5-25 µg or 200-62.5-25 µg inhalation once daily COPD: Dry powder inhaler: one 100-62.5-25 µg inhalation once daily	Safety and efficacy in children <18 years of age have not been established.	Dry powder inhaler: 100-62.5-25 µg 200-62.5-25 µg
Mometasone and formoterol	Asthma: Meter dose aerosol inhaler (HFA): initial, two 100-5 µg or 200-5 µg inhalations BID, starting dose should be based on previous asthma severity, symptom control, and exacerbation risk; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma	Asthma: Meter dose aerosol inhaler (HFA): children five to 11 years of age; two 50-5 inhalations BID	Meter dose aerosol inhaler (HFA): 50-5 µg 100-5 µg 200-5 µg

Generic Name(s)	Usual Adult/Adolescent Dose	Usual Pediatric Dose	Availability
	control; maximum, two 200-5 µg inhalations BID		

*Including bronchitis and/or emphysema.
†Symbicort® 160-4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
‡Advair® 250-50 µg is the only strength FDA-approved for this indication.
BID=twice daily, COPD=chronic obstructive pulmonary disease, HFA=hydrofluoroalkane, QD=once daily

Table 10. Estimated Comparative Daily Doses for the Respiratory Agents-Corticosteroids[23]

Adolescents ≥12 Years of Age and Adults*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	200 to 500	>500 to 1,000	>1,000
Beclomethasone HFA	100 to 200	>200 to 400	>400
Budesonide DPI	200 to 400	>400 to 800	>800
Ciclesonide	80 to 160	>160 to 320	>320
Fluticasone furoate DPI	100		200
Fluticasone propionate HFA	100 to 250	>250 to 500	>500
Fluticasone propionate DPI	100 to 250	>250 to 500	>500
Mometasone HFA	200 to 400		>400
Children 6 to 11 Years of Age*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	50 to 200	>200 to 400	>400
Budesonide DPI	100 to 200	>200 to 400	>400
Budesonide neb	250 to 500	>500 to 1,000	>1,000
Ciclesonide	80	>80 to 160	>160
Fluticasone furoate DPI	50		NA
Fluticasone propionate HFA	50 to 100	>100 to 200	>200
Fluticasone propionate DPI	50 to 100	>100 to 200	>200
Mometasone furoate HFA	100		200
Children 0 to 4 Years of Age*			
Generic Name	**Low Daily Dose (µg)**	**Medium Daily Dose (µg)**	**High Daily Dose (µg)**
Beclomethasone HFA	50 to100 (ages ≥5 years)	Higher doses are associated with an increased risk of local and systemic side-effects, which must be balanced against potential benefits.	
Budesonide neb	500 (ages ≥1 year)		
Fluticasone propionate HFA	50 (ages ≥4 years)		
Mometasone furoate HFA	100 (ages ≥5 years)		

*This is not a table of equivalence, but of estimated clinical comparability, based on available studies and product information.[23]
DPI=dry powder inhaler, HFA=hydrofluoroalkane, NA=not applicable

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory agents-corticosteroids are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Respiratory Agents-Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Tinkelman et al.[28] (2003) Budesonide 100 to 800 µg QD via DPI	OL for 52 weeks following two weeks to five months of treatment in one of four DB, PC studies Adults with persistent asthma not receiving corticosteroids, adults and children previously maintained on ICS, and adults previously maintained on oral corticosteroids	N=1,133 52 weeks	Primary: FEV_1 and oral corticosteroid use Secondary: Plasma cortisol levels and adverse events	Primary: The mean FEV_1 values continued to improve in all patient populations through week six of OL treatment and were sustained for the remainder of the 52-week study. Patients who had not received prior ICS treatment demonstrated the greatest improvement in FEV_1 (67.1±18.0 to 81.2±14.8%). Of the 144 oral corticosteroid-dependent patients, 64 entered the OL study free of oral corticosteroids, and 58 (91%) of those patient remained free of long-term oral corticosteroid use throughout the course of the study. Secondary: There was no evidence of clinically significant suppression of basal or stimulated cortisol levels as a result of treatment with 100, 200 or 400 µg of budesonide BID. Basal and stimulated cortisol levels increased by 20.7±183.3 and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg of budesonide BID. Thirty-three patients discontinued treatment due to adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in four patients, possible in eight patients, likely in one patient, and highly likely in two patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30 patients). No substantial or unexpected changes in vital signs were observed.
Rowe et al.[29] (1999) Budesonide 1,600	DB, PC, RCT Patients 16 to 60 years of age	N=1,006 21 days	Primary: Rates of relapse Secondary:	Primary: The budesonide group experienced fewer relapses (12 patients, 12.8%; 95% CI, 7 to 21) compared to the placebo group (23 patients, 24.5%; 95% CI, 16 to 34) by 21 days (P=0.049). This represents a 48% relapse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/day via DPI vs placebo	presenting to the emergency department with acute asthma who were discharged with a course of oral prednisone (50 mg/day) for seven days		Quality of life, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects and compliance	reduction and suggests as few as nine patients would require treatment with budesonide to prevent one relapse. Secondary: Quality of life scores were higher in the budesonide group compared to the placebo group (P=0.001). The budesonide group used fewer mean albuterol inhalations/day compared to the placebo group (2.4 vs 4.2; P=0.01). The mean and percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, patients in the budesonide group had fewer symptoms of cough (P=0.004), breathlessness (P=0.001), wheezing (P=0.001), and nighttime awakenings (P=0.001) compared to patients receiving placebo. Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at the 21-day follow-up (6.2 vs 5.2; P=0.001). Adverse events were more frequent in the placebo group for both hoarseness and sore throat (P=0.02). The overall incidence of adverse events associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups. Self-reported compliance with the use of oral prednisone was high within the first week of care in both groups (94% for budesonide vs 96% for placebo; P=0.73). Self-reported compliance with budesonide was similar between the groups at seven (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; P=0.95).
Sheffer et al.[30] (2005) START Budesonide 200 to 400 µg QD via	DB, PC, RCT (first three years); OL (following two years) Patients five to 66	N=7,241 5 years	Primary: Time to the first severe asthma-related event, change in post-bronchodilator	Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (HR, 0.56; 95% CI, 0.45 to 0.71; P<0.001). A significant improvement in both pre bronchodilator and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DPI vs placebo Treatment was added to existing asthma therapy.	years of age with mild persistent asthma for less than two years and with no previous regular corticosteroid treatment		FEV_1 percent predicted Secondary: Number of asthma-related events during the DB period, time to first addition of a steroid treatment (systemic or inhaled) during the DB period, symptom-free days, data on healthcare utilization, days off work, and lost school days	postbronchodilator FEV_1 percent values was observed after years one and three of the study for the budesonide treatment group compared to the placebo group. After one year, the differences were 2.24% pre bronchodilator and 1.48% postbronchodilator (P<0.0001 for both) and after three years were 1.71%, (P<0.0001) and 0.88% (P=0.0005), respectively. Secondary: Of the 1,241 serious adverse events reported, 162 in the budesonide group and 276 in the placebo group were related to asthma. Significantly fewer patients in the budesonide group received additional corticosteroids over time compared to the placebo group (31 vs 45%, respectively; P<0.001). An improvement from baseline in symptom-free days occurred for both the budesonide and placebo groups over time. Patients receiving budesonide had significantly more symptom-free days over the three-year study period compared to patients receiving placebo (P<0.001).
Busse et al.[31] (2008) START Budesonide 200 to 400 µg QD via DPI vs placebo Treatment was added to existing asthma therapy. Randomization was for 3 years,	DB, OL, RCT Patients 5 to 66 years of age with mild persistent asthma, with asthma symptoms at least weekly, but not daily, in the 3 months before enrollment, increase in FEV_1 >12% after the use of a SABA, decrease in FEV_1 >15% after exercise challenge, or variation >15% between the 2	N=7,221 5 years	Primary: Change from baseline in postbronchodilator percent predicted FEV_1 Secondary: Change in pre bronchodilator percent predicted FEV_1;the number of SAE; change in asthma-related symptoms; use of concomitant asthma medication to achieve asthma	Primary: During the full five-year study period, the postbronchodilator percent predicted FEV_1 decreased, irrespective of randomized treatment during the DB phase (P=0.74), by an average of 2.22%. However, in adults (age ≥18 years), ignoring sex, there was a statistically significant treatment difference of 0.85% (P=0.044) in favor of budesonide. Secondary: During the full five-year study period, pre bronchodilator percent predicted FEV_1 increased, irrespective of randomized treatment during the DB phase (P=0.20), by an average of 3.24%. The increase was more pronounced in the pediatric age groups (age <18 years) than in adults. In adults, a statistically significant treatment difference of 1.21% (P=0.018) in favor of budesonide was seen between the 2 treatment groups. The incidence rate of SAE decreased in each group over the five-year treatment period. During the three-year DB phase, 315 patients (117 in the budesonide group and 198 in the reference group) experienced one or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by OL treatment for 2 years.	highest and 2 lowest PEF rates in 14 days		control	more SAE, with the risk being significantly lower in the budesonide group than in the reference group (OR, 0.57; P<0.001). Excluding the 315 patients, 30 patients (16 in the budesonide group and 14 in the reference group) experienced one or more SAE during the two-year OL phase, with the risk being similar in the two treatment groups (OR, 1.12; P=0.76). The cumulative risk of having one or more SAE during the full five years of START was significantly lower in the budesonide group than in the reference group (OR, 0.61; P<0.001). The reductions in the percentages of patients with symptoms, restrictions in normal activities, and sleep problems caused by asthma from baseline to the end of the DB treatment phase were maintained or further improved during the subsequent two years of OL budesonide treatment. Between-group differences, which existed during the DB phase, were, however, no longer statistically significant during the OL phase. The percentage of symptom-free days increased among patients in both treatment groups throughout the five-year study period, and the differences between groups were no longer significant during the OL phase. Patients who received budesonide during the DB treatment phase used significantly less additional asthma medication during the OL treatment phase. Significantly fewer patients in the budesonide group required additional ICS (10.4 vs 14.6%; P<0.001) or LABA (6.3 vs 9.3%; P<0.001) in addition to their budesonide treatment by year five.
Agertoft et al.[32] (2000) Budesonide vs control group Patients were enrolled in a one to two-year run-in period where their	PRO Children with asthma	N=332 10 years	Primary: Measured adult height in relation to the target adult height Secondary: Difference between measured height and target adult height in relation to mean cumulative	Primary: The measured and target adult height was 173.2 and 172.9 cm, respectively, in the budesonide group and 173.9 and 174.1 cm, respectively, in the control group. The mean differences between the measured and target adult heights were 0.3 cm (95% CI, -0.6 to 1.2) for the budesonide group, and -0.2 cm (95% CI, -2.4 to 2.1) for the control group. Secondary: Twenty children in the budesonide group did not achieve their adult height. Their mean cumulative dose of 1.25 g was not significantly different from that of children who had attained their adult height, which was 1.35 g (P=0.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
asthma medication was adjusted according to Danish guidelines. Patients considered controlled without continuous ICS use, were then asked to change treatment to budesonide.			budesonide dose, duration of treatment, patient gender, age at beginning of budesonide treatment, age at which adult height was obtained, duration of asthma before budesonide start growth rate of budesonide treatment compared to the run-in period	There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (P=0.16). The difference between measured and target adult heights was not associated with gender (P=0.30), age at the beginning of budesonide treatment (P=0.13), age at which adult height was attained (P=0.82) or duration of asthma before the start of budesonide treatment (P=0.37). Budesonide was associated with a significant change in growth rate during the first years of treatment compared to the run-in period. The mean growth rate was 6.1 cm/year (95% CI, 5.7 to 6.5) during the run-in period, 5.1 cm/year (95% CI, 4.7 to 5.5; P<0.001) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; P=0.02) during the second year of treatment and 5.9 cm/year (95% CI, 5.5 to 6.3; P=0.53) during the third year of treatment. Changes in growth rate during this period were not correlated with the differences between measured and target adult heights (P=0.44). The initial growth retardation was correlated with age, with a more pronounce reduction in younger children (P=0.04). Children with a low SD score for height before budesonide treatment had a smaller adult height than expected (P<0.001).
Baker et al.[33] (1999) Budesonide 0.25 mg BID via nebulizer vs budesonide 0.5 mg BID via nebulizer vs budesonide 1mg AM and placebo	DB, MC, PC, PG, RCT Children, six months to eight years of age, with a diagnosis of asthma	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, PEF and improvements in FEV_1 Secondary: Not reported	Primary: When symptom scores for all active treatment groups were combined, a statistically significant difference between budesonide and placebo was seen as early as day two for nighttime asthma symptoms, and day five for daytime asthma symptoms (P<0.05). There were statistically significant improvements in morning PEF in the budesonide 0.25 mg BID (10.9 L/minute), 0.5 mg BID (24.8 L/minute) and 1 mg QAM (17.1 L/minute) treatment groups compared to placebo (P<0.030 for all) and in evening PEF for each active treatment group (16.8 L/minute for 0.25 mg QAM; P<0.05, 19.2 L/minute for 0.25 mg BID, P<0.05; and 21.0 L/minute for 0.5 mg BID; P<0.010) except 1 mg QAM (14.1 L/minute; P value not reported). All treatment groups experienced a numerical improvement in FEV_1; however, only the improvement with budesonide 0.5 mg BID dose was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PM via nebulizer vs placebo				statistically significant compared to placebo (P=0.031). Secondary: Not reported
Kerwin et al.[34] (2008) (Abstract) Budesonide 400 µg BID (dry powder inhaler [DPI-A]) vs budesonide 360 µg BID (redesigned dry powder inhaler [DPI-B]) vs budesonide 200 µg BID (dry powder inhaler [DPI-A]) vs budesonide 180 µg QD (redesigned dry powder inhaler [DPI-B]) vs placebo	DB, MC, PG, RCT Adult patients with mild to moderate asthma and patients 6 to 17 years of age with mild asthma.	N=1,137 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change is asthma symptoms, β-agonist use, PEF and worsening asthma	Primary: There were significant improvements in FEV_1 for all treatment groups compared to placebo (P<0.05), except DPI-B 180 µg. Secondary: For the adult patients, there were significant greater improvements in all secondary endpoints for all treatment groups compared to placebo (P<0.05). For the pediatric patients, there were significant improvements in PEF in the DPI-B 360 µg BID group compared to placebo (P≤0.011). There were no other significant differences reported. Adverse event profiles were similar for the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sheikh et al.[35] (1999) Flunisolide 1,500 µg/day for a period of one year then crossed over to fluticasone propionate 880 µg/day for one year	AC, OL, XO Children with moderate to severe asthma with a mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\ to\ 75\%}$ and PEFR Secondary: Not reported	Primary: There were significant improvements in all clinical parameters in patients treated with fluticasone propionate compared to patients treated with flunisolide. There was a significant improvement in FVC during the two to six and seven to 12-month periods after switching to fluticasone propionate. Significant improvements were noted in FEV_1 and $FEF_{25\ to\ 75\%}$ at all time points evaluated after switching to fluticasone propionate. There was no significant difference in PEFR between groups at any time period. Secondary: Not reported
Chiu et al.[36] (2014) Budesonide two 200 µg inhalations BID vs ciclesonide two 160 µg inhalations QD	MC, OL, PG, RCT Patients with mild-to-moderate asthma well controlled by a combination of ICS and long-acting β_2-agonist changing to step-down therapy	N=150 12 weeks	Primary: improvement in FEV_1 Secondary: FVC, maximum mid-expiratory flow (MMEF), ACT score, adherence	Primary: The FEV_1 in the ciclesonide group remained stable throughout the treatment period. The FEV_1 (before bronchodilators) of the ciclesonide group (2.2 l; 95% CI, 2.0 to 2.4) was significantly higher than that of the budesonide group (1.9 l; 95% CI, 1.7 to 2.1; P=0.02) at four weeks and at the end of 12 weeks (2.0 l; 95% CI, 1.8 to 2.3; P=0.03) of step-down therapy. Secondary: Patients in the ciclesonide group maintained a stable FVC throughout the 12-week treatment, whereas that of patients receiving budesonide decreased after four weeks of treatment (2.8 l; 95% CI, 2.5 to 3.0 l) compared with baseline (2.9 l; 95% CI, 2.7 to 3.1). However, there was no significant difference between the two groups throughout the 12 weeks of treatment. Patients in the ciclesonide group had a higher rate of treatment adherence (76%) than those in the budesonide group (59%; P=0.03). In the ciclesonide group, patients maintained MMEF, a measurement of the small airway function, during the step-down therapy. The MMEF in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the ciclesonide group was higher than that of the budesonide group (P=0.02). The ACT scores were not significantly different between the two groups at baseline, but improved in the ciclesonide group after four and eight weeks of treatment compared with baseline (P=0.02 and 0.04, respectively).
Vogelmeier et al.[37] (2011) Ciclesonide 160 µg QD All treatment decisions were left to the discretion of the investigator (dose and concomitant rescue medication).	3 MC, OL, OS, PRO Patients 12 years of age and older with persistent, mild to moderate asthma who newly started or switched to treatment with ciclesonide	N=24,037 3 months	Primary: Change from baseline in FEV_1 and symptomatic improvements Secondary: Adverse events and changes in rescue medication use	Primary: The mean FEV_1 was increased from 2.66 L (95% CI, 2.65 to 2.67) at baseline to 3.00 L (95% CI, 2.99 to 3.01) following three months treatment with ciclesonide. This represents an increased from 80.7% (95% CI, 80.5 to 80.9) to 90.1% (96% CI, 89.9 to 90.2) of predicted values. Ciclesonide treatment was associated with a significant increase in PEF of 14% from baseline (from 338 L/min [95% CI, 335 to 340] to 392 L/min [95% CI, 390 to 395]). The concentration of NO significantly decreased from 53.6 PPB (95% CI, 51.8 to 55.4) to 26.2 PPB (95% CI, 25.2 to 27.1), representing a 51% reduction with ciclesonide treatment. The proportion of patients with daily daytime symptoms was reduced from 24.3 to 1.9% after three months of ciclesonide treatment. The proportion of patients with symptoms that occurred >1 day per week was reduced from 59.4 to 24.4% with ciclesonide treatment (P values not reported). The proportion of patients reporting less frequent symptoms (<1 day per week) increased from 14.1 to 68.9% with ciclesonide treatment. A similar improvement was observed for night-time symptoms. The number of nights of the preceding month with nocturnal symptoms decreased from 5.4±5.1 days at baseline to 2.5±2.8 days with ciclesonide treatment. The proportion of patients with impaired sleep quality was reduced from 39.8% at baseline to 8.2% after three months of ciclesonide treatment. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported in 0.2% of patients receiving ciclesonide treatment. Most adverse events were mild or moderate in severity. The most commonly reported adverse events were dysphonia (n=11) and cough (n=10). The proportion of patients with daily use of β_2-agonists decreased from 26.9% at baseline to 8.8% after three months of ciclesonide treatment.
Bateman et al.[38] (2006) Ciclesonide 320 µg BID vs ciclesonide 640 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, were corticosteroid dependant with severe asthma and use of oral prednisone at least every other day for five to six months prior to screening, a history of ICS during the six months prior to screening, use of a β_2-agonist for asthma control the two weeks prior to screening, an FEV_1 between 40 to 80% of predicted normal following a six-hour β_2-agonist treatment withholding period	N=141 12 weeks	Primary: Percent change from baseline in oral prednisone dose Secondary: Percentage of patients who were able to completely discontinue prednisone, change in morning pre-dose FEV_1, change in morning PEF, change in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression and adverse events	Primary: The percent reduction in oral prednisone dose was statistically significant in both treatment groups (-47.39% for the 320 µg BID group; P=0.0001, -62.54% for the 640 µg BID group; P=0.0001 and 4.21% for the placebo group). Secondary: The percent of patients who were able to eliminate their prednisone usage was statistically significant in both treatment groups when compared to the placebo group (29.8% in the 320 µg BID group; P=0.0386, 31.3% in the 640 µg BID group; P=0.0233 and 11.1% in the placebo group). Both treatment groups demonstrated statistically significant improvements in FEV_1 compared to the placebo group (0.17 L for the 320 µg BID group; P=0.0237, 0.17 L for the 640 µg BID group; P=0.0277). Neither treatment group experienced a statistically significant improvement in PEF compared to the placebo group (5.02 L/min for the 320 µg BID group; P=0.5803, 16.67 L/min for the 640 µg BID group; P=0.0736). Neither treatment group experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (P>0.05 for both). The total asthma symptom score (zero to five scale) was not statistically significant compared to the placebo group for either treatment group (change for the 320 µg BID group, 0.33; P=0.2669, change for the 640 µg BID group, -0.07; P=0.8197).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At baseline the percentage of patients with suppressed HPA-axis was 66.0, 60.4 and 62.2% and at week 12 it was 46.8, 43.8 and 53.3% in the 320 µg BID group, 640 µg BID and placebo groups, respectively. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (320 µg BID, 85.1%; 640 µg BID, 79.6%; placebo, 88.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups were aggravated asthma, upper respiratory infection, headache, sinusitis and nasopharyngitis.
Erin et al.[39] (2008) Ciclesonide 320 µg, 1 inhalation QD vs ciclesonide 640 µg, 1 inhalation BID vs placebo	DB, PC, RCT, XO Adults 18 to 45 years of age with stable persistent asthma for ≥6 months and a FEV_1 ≥70% predicted	N=21 7 days	Primary: NO exhalation (two hours after inhalation), pulmonary function test (two to five minutes after inhalation), adenosine monophosphate challenge five hours after inhalation) and sputum induction Secondary: Not reported	Primary: Ciclesonide 320 and 640 µg produced significantly greater improvements in FEV_1 compared with placebo on days one, three, and seven (all P<0.0001). Compared with placebo, ciclesonide 320 and 640 µg improved median exhaled NO levels by -22.6 and -20.7 PPB after seven days, respectively (P<0.001 for both). Although not statistically significant, sputum eosinophils decreased after seven days of ciclesonide treatment. Secondary: Not reported
Stelmach et al.[40] (2016) Ciclesonide 160 µg inhaled QAM vs ciclesonide 320 µg inhaled QAM	DB, PC, PRO, RC Children ages 12 to 18 years of age with a diagnosis of asthma and postexercise symptoms in the past 6 months despite chronic ICS	N=80 8 weeks	Primary: Clinical symptoms as measured by a daily diary card. Secondary: Maximum percentage decrease in FEV_1 after exercise and	Primary: A significant decrease in daytime symptoms from baseline was seen in all groups except the ciclesonide + montelukast group. Mean daily symptoms were scored from 0 points (minimum) to 3 points (maximum). The median daytime symptom scores at baseline verses post study were 0.29 vs 0.19 in the ciclesonide 160 µg group (P=0.0303), 0.57 vs 0.26 in the ciclesonide 320 µg group (P=0.0084), 0.64 vs 0.29 in the ciclesonide + montelukast group (P=0.1213), and 0.43 vs 0.21 in the ciclesonide + formoterol group (P=0.0463). No statistically significant improvement in nighttime symptoms was observed in any of the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ciclesonide 160 µg inhaled QAM and montelukast 5 mg or 10 mg PO QPM vs ciclesonide 160 µg inhaled QAM and formoterol 4.5 µg inhaled QAM and QPM	treatment		FeNO in exhaled breath after exercise.	Secondary: The change from baseline in the maximum decrease in FEV_1 reached the level of significance in all groups except the ciclesonide 160 µg group. The change from baseline in post-exercise FeNO only achieved significance in the ciclesonide 320 µg group.
Brenner et al.[41] (2000) Flunisolide 2 mg/day vs placebo At discharge, all patients were given prednisone 40 mg/d x 5 days and inhaled β-agonists as needed.	PC, RCT Patients 18 to 50 years of age with a diagnosis of asthma presenting to the emergency department with an acute asthma exacerbation	N=104 24 days	Primary: PEFR Secondary: Overall symptoms and albuterol use	Primary: PEFR was similar between the two groups throughout the trial (P=0.36 on day 24). There was a mean difference of 4 units, favoring flunisolide, between the groups (95% CI). Secondary: Both symptoms and albuterol use were similar in both groups for the duration of the trial. 75% of patients in the flunisolide group reported symptom improvement vs 70% in the placebo group (95% CI, -17 to 27).
Lee-Wong et al.[42] (2002) Flunisolide 2,000 µg BID via spacer	DB, PC, RCT Patients 18 to 55 years of age admitted to the emergency	N=40 7 days	Primary: PEFR, FEV_1 Secondary: Change in asthma symptom scores	Primary: From day one to day seven, mean PEFR increased from 190 to 379 L/min in the ICS group, and from 207 to 347 L/min in the prednisone group (P=0.95; 95% CI, -66.3 to ∞). Mean FEV_1 increased from 1.6 to 2.3 L in the ICS group and from 1.4 to

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vs placebo Patients were also randomized to receive oral prednisone or placebo.	department for an acute asthma exacerbation			2.1 L in the prednisone group (P=0.33; 95% CI, -21.7 to ∞). Secondary: Mean symptom scores declined from 1.4 to 0.7 in the ICS group and decreased from 1.3 to 0.4 in the prednisone group (P=0.39).
O'Byrne et al.[43] (2014) Fluticasone furoate 50 µg inhaled QPM vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and treatment with non-ICS, FEV_1 ≥60% predicted, and reversibility with albuterol or salbutamol	N=248 12 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily morning and evening PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients controlled, AQLQ total score, ease of use of the ELLIPTA® dry powder inhaler	Primary: Pre-dose FEV_1 at week 12 for the fluticasone furoate group was 157 mL as compared to 38 mL in the placebo group, resulting in a treatment difference of 120 mL (P=0.012). The per protocol population was similar, with a treatment difference in favor of fluticasone furoate 50 mcg of 131 mL; 95% CI, 38 to 224; P=0.006). Secondary: There was a significant improvement in the percentage of rescue-free 24-hour periods in patients treated with fluticasone furoate (28.7%) compared to placebo (17.1%), resulting in a treatment difference of 11.6% (P=0.004). This equated to an additional 0.8 rescue-free 24-hour periods per week with fluticasone 50 µg treatment. Change from baseline in evening PEF over the 12-week treatment period was increased with treatment with fluticasone furoate 50 µg (22.8 L/min) and placebo (19.5 L/min), but the treatment difference (3.3 L/min) was not statistically significant (P=0.536). Due to this, significance could not be inferred for the remaining endpoints. Morning PEF was numerically increased and greater for fluticasone furoate 50 µg (34.5 L/min) compared with placebo treatment (22.9 L/min; treatment difference of 11.6 L/min). Increase from baseline in the percentage of symptom-free 24-hour periods was also numerically greater for fluticasone furoate 50 µg (22.6%) compared with placebo treatment (14.0%; treatment difference of 8.6%), which equates to an additional 0.6 symptom-free 24-hour periods per week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with fluticasone furoate treatment. A numerically greater proportion of patients in the placebo group withdrew due to lack of efficacy (14%) compared with patients in the fluticasone furoate 50 µg group (6%) Numerically greater increases in ACT scores, proportion of patients with an ACT score ≥20 and change from baseline in total AQLQ scores were observed for fluticasone furoate 50 µg compared with placebo. At baseline, most patients were able to use the ELLIPTA® inhaler correctly after being instructed once (98% fluticasone furoate; 96% placebo). At week four, most patients rated the ELLIPTA® inhaler as 'easy/very easy' to use (97%) and 'easy/very easy' to see how many doses of medication were left in the inhaler (95%).
Woodcock et al.[44] (2011) Fluticasone furoate 200 µg inhaled QAM vs fluticasone furoate 400 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma, FEV_1 50 to 80% predicted, and reversibility with inhaled salbutamol	N=545 8 weeks	Primary: Pre-dose FEV_1 Secondary: Safety	Primary: Pre-dose FEV_1 was significantly improved for each of the fluticasone furoate treatment arms compared to placebo at week eight (P=0.033 for 200 µg once-daily arms, P<0.001 for 400 µg once daily and 200 µg twice daily arms). Fluticasone furoate 400 µg once daily in the evening resulted in similar placebo-adjusted improvements in evening pre-dose FEV_1 at week eight compared with 200 µg twice daily (240 mL compared with 235 mL). Fluticasone furoate 200 µg twice daily resulted in greater improvements in placebo-adjusted morning pre-dose FEV_1 than 400 µg once daily in the morning at week eight (315 mL compared with 202 mL). A ≥200 mL increase in placebo-adjusted pre-dose FEV_1 was observed for the 400 µg once daily in the morning or evening groups and for 200 µg twice daily group but not for either of the 200 µg once daily groups. However, the increase from baseline was ≥200 mL with both 200 µg once daily groups. Results for the per protocol population were consistent with those of the intention to treat population; although, the relative treatment effect of all active treatment groups was generally lower. The effect of fluticasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400 µg inhaled QPM vs fluticasone furoate 200 µg inhaled BID vs placebo				furoate 200 µg once daily in the evening FEV_1 was not significantly different from placebo (P=0.264). Secondary: The proportion of patients who reported any adverse event during the treatment period was 28% in the placebo group and 31 to 39% in the active treatment groups. The most frequently reported adverse events during treatment were headache (6 to 9%), nasopharyngitis (3 to 8%), bronchitis (0 to 4%), pharyngolaryngeal pain (<1 to 3%), and upper respiratory tract infection (<1 to 3%). The incidence and type of adverse events were generally similar to placebo and the frequency of adverse events did not appear to be related to the dose of fluticasone furoate. A total of four serious adverse events were reported, with angioedema the only one considered to be possibly related to the study drug. A total of 11 patients reported 13 adverse events that resulted in study withdrawal: three patients in the 200 µg once-daily morning group, one in the 200 µg once-daily evening group, three in the 400 µg once-daily morning group, three in the 400 µg once-daily evening group and one in the 200 µg twice-daily group. There were no safety concerns related to vital signs, or laboratory safety tests. No treatment-related changes were apparent. The incidence of oral candidiasis was low in the active treatment groups (0%to 4% compared with <1% for placebo) as was the incidence of asthma exacerbations (<1 to 4% compared with 14% for placebo).
Medley et al.[45] (2012) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate	DB, DD, MC, PC, PG, RCT Patients 16 to 55 years of age with a diagnosis of persistent asthma and PEF 50 to 90% predicted; reversibility with	N=578 28 days	Primary: Change from baseline in pre-treatment daily trough PEF between morning and evening doses Secondary: FEV1, PEF,	Primary: The mean difference in trough PEF between fluticasone furoate 100 µg once daily in the morning compared with 100 µg once daily in the evening was 13.4 L/min (95% CI, 2.3 to 24.4). However, the placebo response was greater in the morning than in the evening (18.8 L/min compared with 8.8 L/min. All fluticasone furoate groups were associated with a statistically significant improvement in trough PEF compared to placebo (P<0.001 for 100 µg QAM and 250 µg QPM, P=0.005 for 100 µg QPM). There was an indication that the 250 µg once daily in the evening produced greater increases in PEF than 100 µg once daily in the evening (by 6.7 L/min), but

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs placebo BID (QAM and QPM)	inhaled salbutamol		percentage of symptom-free 24-hour periods, symptom-free days and nights, nights with no awakenings, rescue medication-free 24-hour periods, and withdrawals due to lack of efficacy, adverse events	the difference was not statistically significant. Secondary: Analyses of change from baseline in pre-dose FEV_1 found substantial improvements from baseline in FEV_1 that were greater with fluticasone furoate (203 to 317 mL) than with placebo (99 mL). However, statistical superiority of any dose was not demonstrated. When compared to placebo, fluticasone propionate was associated with a significant reduction in symptoms, rescue medication taken, and night-time awakenings (all P<0.001; except: P=0.001 for percent symptom-free days with 100 µg evening; P=0.006 for percent symptom-free nights with 100 µg in the morning, and P=0.002 for percent rescue medication-free days with 100 µg in the evening). Analysis of the effect of fluticasone furoate 250 µg once daily in the evening compared to 100 µg once daily in the evening indicated a greater improvement with 250 µg once daily in the evening in 24-hour symptom-free periods, rescue medication-free 24-hour periods, and night-time awakenings, but the differences were not significant. Three patients withdrew from the study due to lack of efficacy (other than exacerbations); two on placebo and one on fluticasone furoate 100 µg once daily in the morning. The number of withdrawals with fluticasone furoate was not statistically significant compared to placebo. The proportion of patients reporting an adverse event during the treatment period was 26% in the placebo group and 23 to 26% with fluticasone furoate. Rates of occurrence of the most frequent adverse events (≥3% of patients in any treatment group) and treatment-related adverse events were low and similar across the treatment groups. The most frequently reported AEs during treatment were headache (4 to 9%) and nasopharyngitis (3 to 4%). None of the three serious adverse events were considered related to study treatment and all were resolved within three weeks after withdrawal. No clinically significant abnormalities or shifts from baseline were observed in any treatment group for hematological, clinical chemistry, vital signs, or ECG parameters. The incidence of oropharyngeal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				candidiasis was low (≤3% of patients in any treatment group), with slightly higher incidence (3% [4 patients]) in the 250 µg group than in any of the other three groups.
Wooodcock et al.[46] (2014) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and stable use of any ICS dose for ≥12 weeks or for ≥ 4 weeks for mid-high dose, FEV_1 40 to 90% predicted and reversibility with albuterol	N=238 24 weeks	Primary: Pre-dose (trough) FEV_1 at week 24 Secondary: Percentage of rescue-free and symptom-free 24-hour periods, change in PEF average, ACT scores	Primary: Both strengths of fluticasone furoate were associated with improvements in trough FEV_1 of >200 mL from baseline at week 24. A numerically greater increase was observed with the fluticasone furoate 200 µg dose than with 100 µg dose (treatment difference, 77 mL; 95% CI, -39 to 192). Repeated-measures analysis of change from baseline in trough FEV_1 over 24 weeks of treatment showed that improvement in trough FEV_1 was apparent within two weeks of randomization and was maintained throughout the treatment period. Secondary: Improvements over 24 weeks in percentage of rescue-free and symptom-free 24-hour periods and PEF, as well as in ACT score at week 24, were observed in both treatment groups. No treatment differences were observed in incidence of severe asthma exacerbations or healthcare resource utilization. There were no asthma-related inpatient hospitalizations.
van den Berge et al.[47] (2010) Fluticasone furoate 1,000 µg inhaled 2, 14, or 26 hours prior to measure of eNO and PC_{20} AMP vs fluticasone propionate 1,000	MC, DB, PC, PG, RCT, XO (six-way) Patients 18 to 55 years of age diagnosed with asthma, FEV_1 >70% predicted, PC_{20} AMP< 50 mg/mL, presence of atopy	N=24 8 weeks	Primary: PC_{20} AMP, eNO Secondary: Adverse reactions	Primary: Fluticasone furoate significantly improved the PC_{20} AMP at all time points compared to placebo. The mean difference in doubling concentrations being 2.18 (95% CI, 1.13 to 3.23), 1.54 (95% CI, 0.48 to 2.59), and 1.30 (95% CI, 0.26 to 2.34) at two, 14, and 26 hours, respectively (P<0.05 for all time points). Fluticasone propionate significantly improved the PC_{20} AMP at 14 hours but not at 26 hours compared to placebo. The difference in doubling concentrations being 1.72 (95% CI, 0.70 to 2.75; P<0.05) and 0.33 (95% CI, −0.69 to 1.34; P value not reported) at 14 and 26 hours respectively. No significant changes in the concentration of eNO were observed after treatment with fluticasone furoate or propionate at any time point.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg inhaled 14 or 26 hours prior to measure of eNO and PC_{20} AMP vs placebo Each treatment period was separated by at least five days and a maximum of 10 days.				Secondary: The most frequently occurring adverse event was bronchospasm (33%), followed by dyspnea, dizziness, headache, nausea, palpitations and fatigue. None of the adverse events occurred more frequently during treatment with fluticasone furoate when compared to fluticasone propionate or placebo.
Bleecker et al.[48] (2011) Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 300 µg inhaled QPM vs fluticasone furoate	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with moderate persistent symptomatic asthma while receiving low-dose ICS therapy (for at least eight weeks); reversibility to albuterol, pre-bronchodilator FEV_1 of 40% to 90% predicted	N=622 8 weeks	Primary: Pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to lack of efficacy, safety	Primary: At week eight, all active treatment groups demonstrated significant placebo-adjusted improvements from baseline in predose FEV_1 ($P<0.001$) and achieved the predefined 200 mL difference from placebo. Improvements with fluticasone furoate were similar to or greater than those reported for twice-daily fluticasone propionate. The treatment interaction with each of the covariates modeled was not statistically significant. Similar results were obtained for the per-protocol population. Secondary: Morning and evening predose PEF values over weeks one through eight were also significantly different from placebo, indicating greater improvement with therapy (morning PEF, $P<0.001$ for all doses; evening PEF, $P=0.18$ for fluticasone furoate and $P<0.001$ for all other active treatments). Mean symptom- and rescue-free 24-hour periods increased over eight weeks in all groups. Significant improvements in symptoms were observed with fluticasone furoate 400 µg once daily and fluticasone propionate 250 µg twice daily, and for rescue use with all treatments except fluticasone furoate 200 µg once daily (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo				Withdrawals attributable to lack of efficacy were significantly greater with placebo (33%) compared with all fluticasone furoate treatment groups (10, 11, 8, and 7% for 100, 200, 300, and 400 µg, respectively; P<0.001) and twice-daily fluticasone propionate 250 µg (14%; P=0.002). On-treatment adverse events were reported in 33 to 41% of patients across the fluticasone furoate groups, 42% with fluticasone propionate and 30% with placebo. The most commonly reported on-treatment adverse events were headache (6 to 9% across treatment groups) and nasopharyngitis (4 to 9%). No dose-related increases in the frequency of the most common adverse events were observed. The incidence of oral/oropharyngeal candidiasis across the fluticasone furoate groups was less than 1 to 4%, 4% with fluticasone propionate 250 µg, and 0% with placebo.
Busse et al.[49] (2011) Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone furoate 600 µg inhaled QPM vs fluticasone furoate 800 µg inhaled QPM	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with persistent asthma not controlled using medium-dose ICS, FEV_1 of 40 to 90% predicted; reversibility of asthma with inhaled salbutamol	N=627 8 weeks	Primary: Pre-dose FEV_1 Secondary: Asthma symptom scores, rescue salbutamol use, morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to worsening asthma	Primary: Pre-dose FEV_1 was significantly improved in all active treatment groups when compared with placebo at week eight (P<0.001). The predefined 200 mL difference relative to placebo was achieved in all fluticasone furoate groups. Secondary: All active treatments provided significant improvement from baseline in evening PEF over the eight-week treatment period (P<0.001). Similar improvements for all active treatments were also observed in morning PEF and were significantly improved when compared with placebo (P<0.001). Based on patient-reported data, the proportion of symptom-free 24-hour periods during weeks one to eight increased relative to baseline in all study groups and was greater with all active treatments than placebo (P<0.001, P<0.001, P=0.022, and P=0.002 for fluticasone furoate 200 µg, 400 µg, 600 µg, and 800 µg, respectively; P=0.017 for fluticasone propionate). Similar significant improvements were observed for rescue-free 24-hour periods in the treatment groups compared to placebo (P<0.001 for all). The proportion of patients with symptom-free and rescue-free days were also significantly greater in the all treatment groups than in the placebo group (comparisons with placebo P<0.001, except for P=0.006 with fluticasone furoate 600 µg for symptom-free days).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate 500 µg inhaled BID vs placebo				Withdrawal rates due to lack of efficacy were significantly lower in all active treatment groups compared with the placebo group (6 to 12% compared with 33%; P<0.001 for all comparisons). The fewest withdrawals due to lack of efficacy occurred in the fluticasone furoate 400 µg and fluticasone propionate groups (6 and 7%, respectively). Overall, fluticasone furoate was well tolerated; 31% to 35% of patients in the fluticasone furoate groups and 22% in the placebo group experienced one or more adverse event during treatment. The most frequently reported adverse events were oral candidiasis (<1 to 12%), headache (3 to 11%), nasopharyngitis (2 to 7%) and dysphonia (<1 to 5%). The incidence of drug-related adverse events was 2% in the placebo group and 11, 11, 3, 17, and 9% of patients in the fluticasone furoate 200, 400, 600, and 800 µg groups and fluticasone propionate group, respectively; the most frequent of these were oropharyngeal candidiasis, oral candidiasis, and dysphonia. The frequency of these events was similar in all active treatment groups, with the exception of oral candidiasis, which occurred most frequently in the fluticasone furoate 800 µg group. The incidence of asthma exacerbations was lower in the active treatment groups (<1 to 6%) than in the placebo group (16%). Most exacerbations in the placebo group were attributed to lack of efficacy. Eight percent of patients in the placebo arm required oral corticosteroids compared with 0 to 2% in the fluticasone furoate groups and 3% in the fluticasone propionate group. Three patients were hospitalized due to asthma exacerbation, one each in the placebo, fluticasone furoate 200 µg once daily and fluticasone propionate 500 µg twice daily arms.
Bateman et al.[50] (2012) Fluticasone furoate 25 µg inhaled QPM vs fluticasone furoate	AC, DB, DD, MC PC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma, FEV_1 40 to 90% predicted, and not adequately	N=598 8 weeks	Primary: Pre-dose evening FEV_1 Secondary: PEF average, percentage of symptom-free 24-hour periods, rescue-free 24-	Primary: A significant dose–response relationship for change in pre-dose evening FEV_1 (baseline to week eight) was achieved across once-daily fluticasone furoate (25 to 200 µg) both when placebo was included (P<0.001) and when placebo was not included (P=0.03). At week eight, all active treatment groups showed a >200 mL improvement in pre-dose FEV_1 from baseline; the fluticasone furoate 100 µg and 200 µg once daily doses achieved a >200 mL difference compared with placebo (P<0.001). Fluticasone furoate 50 µg once daily, although

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QPM fluticasone furoate 200 µg inhaled QPM vs fluticasone propionate 25 µg inhaled BID vs placebo	controlled on SABAs (or other non-steroidal controllers) that they had been using for ≥3 months		hour periods and number of withdrawals due to lack of efficacy, safety	failing to reach the pre-defined 200 mL difference, was also significantly better than placebo (P<0.05). Fluticasone furoate 25 µg and fluticasone propionate failed to show superiority compared with placebo (P value not reported). Secondary: Evening PEF improvements from baseline were largest in the fluticasone furoate 50 µg and 200 µg once-daily groups (mean difference 20.7 and 21.7 L/min, respectively, compared with placebo; P<0.001). Significant but smaller differences were also achieved with fluticasone furoate 25 µg once daily (14.0 L/min, P=0.019) and 100 µg once daily (16.1 L/min, P=0.005) and were of a similar magnitude to the fluticasone propionate 100 µg twice daily group (14.9 L/min; P=0.011). Similarly, all active treatment groups improved morning PEF relative to baseline and these changes were significantly greater than with placebo (P values not reported). Fluticasone furoate 200 µg once daily exhibited the greatest difference in morning PEF (22.0 L/min; P<0.001). For symptom-free periods, fluticasone furoate 100 µg once daily demonstrated the greatest increase from baseline relative to placebo (20.2%). Fluticasone furoate 50 µg and 200 µg once daily showed numerically lower increases, similar in magnitude to the fluticasone propionate 100 µg twice-daily group. For all except the fluticasone furoate 25 µg once-daily group, the effect was significantly better than for placebo (P values not reported). A similar pattern was evident for rescue-free periods (P values not reported). Withdrawal rates due to lack of efficacy were highest in the placebo and fluticasone propionate twice-daily groups (15% and 11%, respectively). Rates for fluticasone furoate once-daily ranged from 3 to 9%. The differences in the fluticasone furoate 50 µg (3%) and 100 µg (5%) once-daily groups were significantly lower than for placebo (P=0.004 and P=0.032, respectively). Overall, 26%, 34%, and 20% to 32% of patients in the placebo, fluticasone propionate twice-daily and fluticasone furoate once-daily groups, respectively, reported at least one on-treatment adverse events. Drug-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				related adverse events were low in all groups (0 to 6%), with no apparent dose-dependent events.
Woodcock et al.[51] (2011) Fluticasone furoate 200 µg QD for 28 days and fluticasone propionate 100 µg BID for 28 days and placebo vs Fluticasone furoate 200 µg QD for 28 days and fluticasone furoate 100 µg BID for 28 days and placebo Twelve sequences	AC, DB, MC, PC, RCT, XO Patients ≥12 years of age with moderate persistent asthma, FEV_1 40 to 80% predicted and reversibility to inhaled salbutamol	N=190 28 days (per period)	Primary: Pre-dose FEV_1 at day 28 of each treatment period Secondary: Safety	Primary: Pre-dose FEV_1 increased in all groups, but the mean increases in the four active treatment groups were approximately twice those in the placebo group. The differences compared to placebo were statistically significant in all four active treatment groups, as assessed in the ITT population ($P<0.001$ for fluticasone furoate 200 µg once daily, fluticasone furoate 100 µg twice daily and fluticasone propionate 100 µg twice daily; $P=0.02$ for the fluticasone propionate 200 µg once daily). In the ITT population, the lower 95% CI for the mean difference between fluticasone furoate 200 µg once daily and 100 µg twice daily in pre-dose FEV_1 on day 28 was -35 mL (LS mean difference of 11 mL). This difference was within the pre-defined limit of -110 mL, thus demonstrating non-inferiority of the fluticasone furoate 200 µg once-daily regimen. Similar results were obtained from the non-inferiority analysis in the PP population. Data from patients treated with fluticasone propionate indicated numerically reduced improvement in pre-dose FEV_1 with the 200 µg once-daily dose in comparison with 100 µg twice daily, although no statistical comparison of these groups was performed. Secondary: No serious adverse events were reported and no adverse events led to permanent discontinuation of drug or to patient withdrawal. The frequency of on-treatment adverse events was higher in the fluticasone furoate 200 µg once-daily, fluticasone furoate 100 µg twice-daily and dry powder inhaler placebo groups (16, 18, and 14%, respectively) than in the fluticasone propionate 200 µg once-daily, fluticasone propionate 100 µg twice-daily and diskus placebo groups (5, 7, and 12% respectively). Upper respiratory tract infections were the most commonly reported adverse event, occurring in 5% of patients in each of the fluticasone furoate groups and 1% in the placebo group; no other AEs were reported by more than 1% of patients in either of the fluticasone furoate groups or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
comprising three 28-day treatment periods. Patients received either a fluticasone furoate plus placebo regimen or a fluticasone propionate plus placebo regimen. The order of receiving different periods is varied by sequence.				the placebo group during the treatment period. However, only three of the adverse events reported, headache, dry throat, and tachycardia, were considered to be potentially drug-related. One patient reported dysphonia in the fluticasone propionate 200 µg once daily group. There were no cases of oral candidiasis. Asthma exacerbations occurred in five (3%) patients on placebo, and one (<1%) patient on fluticasone furoate 200 µg once daily. None of the exacerbations were severe enough to require hospitalization.
Lötvall et al.[52] (2014) Fluticasone furoate 100 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo QPM or BID	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40 to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=343 24 weeks	Primary: Pre-dose FEV_1 at 24 weeks Secondary: Mean change in percentage of rescue-free 24-hour periods, PEF and percentage of symptom-free 24-hour periods over the 24 weeks, change in AQLQ score at weeks 12 and 24, Asthma Control Test score at weeks 12 and 24 and withdrawal due to lack of efficacy	Primary: Pre-dose evening FEV_1 was significantly improved at week 24 with fluticasone furoate 100 µg QPM and fluticasone propionate 250 µg BID when compared to placebo (P=0.009 and P=0.011, respectively); both active treatments resulted in similar effects compared with placebo. Secondary: The percentage of rescue-free 24-hour periods was significantly increased compared with placebo for both fluticasone furoate µg QPM and fluticasone propionate 250 µg BID (P<0.001). Initial analysis of evening PEF found no significant difference between placebo and active therapy. Because of the step-down closed testing procedure employed, significance could not be inferred for all subsequent efficacy comparisons regardless of P value. Morning PEF, percentage of symptom-free 24-h periods over the course of the study and AQLQ at weeks 12 and 24 were numerically improved by both active treatments compared with placebo (P value not reported).
Busse et al.[53] (2014)	AC, DB, DD, MC, PC, PG, RCT	N=222	Primary: Pre-dose (trough)	Primary: Improvement in change from baseline of FEV_1 at week 24 for fluticasone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone furoate 50 µg inhaled QPM vs fluticasone propionate 100 µg inhaled BID vs placebo	Patients ≥12 years of age with a diagnosis of asthma for ≥12 weeks, treatment with non-ICS controllers or short-acting beta agonists, FEV_1 ≥60% predicted, and reversibility with salbutamol	24 weeks	FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily AM and PM PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients with ACT score ≥20, change in total AQAQ score, and unscheduled asthma-related healthcare resource utilization	furoate was not statistically significant when compared to placebo (37 mL, P=0.430). When fluticasone propionate was compared to placebo, there was a significant improvement in favor of the active treatment (102 mL, P=0.030). Because of the lack of statistical significance on the primary endpoint, all subsequent endpoints were interpreted as descriptive only for the fluticasone furoate group when compared to placebo treatment. Secondary: The percentage of rescue-free 24-hour periods increased from baseline over weeks 0 to 24 in all treatment groups; mean improvements compared to placebo, were not statistically significant for fluticasone furoate (7.8%; 95% CI, −1.0 to 16.7), but were significant for fluticasone propionate (10.6%; 95% CI, 1.7 to 19.6). The number of additional rescue-free days per week compared to placebo was similar for fluticasone furoate (0.5) and fluticasone propionate (0.7). Mean change from baseline in evening PEF over the 24-week study for fluticasone furoate compared to placebo was 17.2 L/min (95% CI, 5.9 to 28.6) and 4.3 L/min (95% CI, −7.0 to 15.7) for fluticasone propionate compared to placebo. Change in morning PEF compared to placebo was 19.2 L/min (95% CI, 8.5 to 29.9) for and 10.6 L/min (95% CI, −0.2 to 21.3) for fluticasone propionate. Changes from baseline in percentage of symptom-free 24-hour periods for fluticasone furoate and fluticasone propionate when compared to placebo were 8.3 (95% CI, 0.3 to 16.3) and 7.5 (95% CI, −0.5 to 15.5), respectively. The equivalent number of additional symptom-free days per week compared to placebo was similar for fluticasone furoate (0.6) and fluticasone propionate (0.5). There were more withdrawals due to lack of efficacy with placebo (20%) than with fluticasone furoate (12%) or fluticasone propionate (8%).
Bleecker et al.[54] (abstract) (2014) Fluticasone furoate	DB, PC, PG, RCT Patients ≥12 years of age with a diagnosis of	N=609 12 weeks	Primary: Pre-dose (trough) FEV_1, and serial (0 to 24 hours) $wmFEV_1$	Primary: When compared with placebo, trough FEV_1 was significantly improved in both the fluticasone furoate and fluticasone furoate/vilanterol groups (placebo, 196 mL; fluticasone furoate, 136 mL; P=0.002; fluticasone furoate/vilanterol, 172 mL; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 µg inhaled QPM vs fluticasone furoate/vilanterol 100/25 µg inhaled QPM vs placebo QPM	persistent asthma		Secondary: Rescue-free 24-hour periods, safety	There was also a significant difference in serial (0 to 24 hours) $wmFEV_1$ for both treatment groups when compared to placebo. The serial (0 to 24 hour) $wmFEV_1$ for the placebo group was 212 mL as compared to 186 mL in the fluticasone furoate group (P=0.003) and 302 mL in the fluticasone furoate/vilanterol (P=<0.001). When fluticasone furoate/vilanterol was compared to fluticasone furoate, treatment differences approached significance for serial wmFEV1 (116 mL; P=0.060), but not for trough FEV1 (36 mL; P=0.405). Secondary: The percentage of rescue-free 24-hour periods with fluticasone furoate/vilanterol was 10.6% greater than fluticasone furoate and 19.3% greater than placebo. Urinary cortisol suppression was observed with fluticasone furoate/vilanterol (ratio, 0.82) relative to placebo (P=0.032), but not with fluticasone furoate (no P value reported). Adverse event and safety profiles were similar across treatment groups.
O'Byrne et al.[55] (2014) Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate-vilanterol 200-25 µg inhaled QPM vs	AC, DB, DD, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=586 24 weeks	Primary: Pre-dose FEV_1 and $wmFEV_1$ (0 to 24 hours post-dose) Secondary: Mean change in percentage of rescue-free 24-hour periods, percentage of symptom-free 24-hour periods and total AQLQ score after 12 and 24 weeks	Primary: Trough FEV_1 at week 24 was improved from baseline with all active therapies. The differences between fluticasone furoate-vilanterol and fluticasone furoate, and fluticasone furoate-vilanterol and fluticasone propionate were both significant (P<0.001 for both), while fluticasone furoate was noninferior to fluticasone propionate. Change from baseline in trough FEV_1 by treatment showed sustained benefit with fluticasone furoate/vilanterol over fluticasone furoate and fluticasone propionate at all study time-points. The $wmFEV_1$ from 0 to 24 hours post-dose at week 24 compared with baseline was improved in all treatment arms. When compared to the single entity fluticasone furoate and fluticasone propionate, fluticasone furoate-vilanterol significantly improved $wmFEV_1$ 0 to 24 hours post-dose (P=0.048 and P=0.003, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate 500 µg inhaled BID				Secondary: The percentage of rescue-free 24-hour periods increased over the study with all therapies. The difference in improvement was significant for the comparison of fluticasone furoate-vilanterol with fluticasone furoate, but not for fluticasone furoate-vilanterol compared with fluticasone propionate (P<0.001 and P=0.067, respectively). The percentage of symptom-free 24-hour periods increased over the course of the study. Fluticasone furoate-vilanterol provided a significant improvement when compared to fluticasone furoate but not fluticasone propionate (P=0.010 and P=0.137, respectively). Improvements from baseline in the AQLQ score were seen in all treatment groups at week 24. The improvements were similar in each arm and were not statistically significant. Over the 24-week treatment period, fewer patients withdrew due to lack of efficacy in the fluticasone furoate-vilanterol group (3%) compared with the fluticasone furoate (11%) or fluticasone propionate (9%) groups.
Lin et al.[56] (2016) Fluticasone furoate and vilanterol 100/25 µg inhaled QPM via DPI vs placebo	DB, MC, PC, PG, RCT Asian patients ≥ 12 years of age (≥ 18 in some centers based on local regulations) with a diagnosis of asthma, morning FEV1 of 40 to 90% of predicted, and uncontrolled symptoms despite low to mid-strength ICS or low-dose ICS/LABA.	N= 311 12 weeks	Primary: Mean change from baseline in daily evening PEF Secondary: Mean change from baseline in percentage of rescue-free 24-hour periods, daily morning PEF, percentage of symptom-free 24-hour periods, AQLQ 12 score, AEs, and severe exacerbations.	Primary: There was an increase in daily evening PEF from baseline in the fluticasone furoate-vilanterol group (mean ± SE, 39.2 ± 3.14 L/min) and a decrease from baseline in the placebo group (mean ± SE, -11.8 ± 3.16 L/min). The adjusted treatment difference for the fluticasone furoate/vilanterol group compared to the placebo group was 51.0 L/min (95% CI, 42.2 to 59.7 L/min; P <0.001). Secondary: There was an improvement from baseline in the percentage of rescue-free 24-hour periods in both the fluticasone furoate-vilanterol and placebo groups (LS mean 30.1 and 8.3, respectively), percentage of symptom-free 24-hour periods (LS mean 24.8 and 9.0, respectively), and overall AQLQ 12 scores (LS mean 0.84 and 0.33, respectively). For daily morning PEF (L/min), there was an improvement from baseline with furoate-vilanterol and deterioration from baseline with placebo (LS mean 43.6 and -9.3, respectively). The adjusted treatment differences for furoate-vilanterol versus placebo were statistically significant (P< 0.001) for all of these

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				secondary end points. The incidence of adverse events with treatment was 35% with fluticasone furoate-vilanterol and 31% with placebo. The most frequently reported adverse event was upper respiratory tract infection (reported by 7% in the fluticasone furoate/vilanterol group and 9% in the placebo group). Severe asthma exacerbations were reported for one patient in the furoate/vilanterol group and seven patients in the placebo group.
Bateman et al.[57] (2014) Fluticasone furoate- vilanterol 100-25 µg QD vs fluticasone furoate 100 µg QD Patients replaced their current short-acting bronchodilator and used albuterol/salbutamol as-needed for symptoms	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma for ≥1 year and documented use of ICS or ICS/LABA for ≥12 weeks with a stable dose for ≥ 4 weeks, ≥1 asthma exacerbation in the previous year, FEV_1 of 50 to 90% predicted	N=2019 24 to 78 weeks	Primary: Time to first severe asthma exacerbation Secondary: Rate of severe asthma exacerbations per patient per year and change from baseline at week 36 in evening trough FEV_1	Primary: Fluticasone furoate-vilanterol significantly delayed the time to first severe exacerbation relative to fluticasone furoate. The adjusted probability of experiencing a severe asthma exacerbation by 52 weeks was 15.9% (95% CI, 13.5 to 18.2%) in the single agent group and 12.8% (95% CI, 10.7 to 14.9%) in the combination group. The HR for combination vs fluticasone furoate alone was 0.795 (95% CI, 0.642 to 0.98; P=0.036, adjusted for the interim analysis). Secondary: The rate of severe asthma exacerbations per patient per year was significantly lower in the combination group than in the fluticasone furoate group (0.14 vs 0.19). Trough FEV_1 increased over the treatment period in both treatment groups. Fluticasone furoate- vilanterol demonstrated statistically significant improvements over fluticasone furoate in trough FEV_1, with adjusted mean changes of 83 to 95 mL (P<0.001).
Woodcock et al.[58] (2013) Fluticasone furoate-vilanterol 100-25 µg QD vs	DB, DD, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12	N=806 24 weeks	Primary: Change from baseline in $wmFEV_1$ after 24 weeks Secondary: FEV_1 assessments,	Primary: Improvements from baseline in 0- to 24-hour $wmFEV_1$ were seen in both groups; however, the adjusted mean treatment difference was not statistically significant. Secondary: There were no differences in key secondary end points.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate-salmeterol 250-50 µg BID	weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 85% predicted; reversible on inhalation of albuterol		time to onset of bronchodilator effect, AQLQ	
Bernstein et al.[59] (2018) Fluticasone furoate-vilanterol 100-25 µg once-daily (FF/VI) vs fluticasone propionate-salmeterol 250-50 µg BID (FP/SAL) vs fluticasone propionate 250 µg twice-daily	DB, DD, MC, RCT patients ≥12 years of age with an asthma diagnosis, FEV_1 ≥80% predicted, and have received treatment with ICS/LABA either as combination or separate inhalers for at least 12 weeks	N=1,504 24 weeks	Primary: Change from baseline in evening trough FEV_1 Secondary: Change from baseline to 24 weeks in the percentage of rescue-free and symptom-free 24-hour periods, and morning and evening PEF, as well as the percentage of patients with controlled asthma (defined as an ACT score ≥20)	Primary: At Week 24, the treatment difference between FF/VI and FP/SAL for evening trough FEV_1 was 19 mL (95% CI, −11 to 49) in the intent-to-treat population and 6 mL (95% CI, −27 to 40) in the per-protocol population. In both populations, the lower bound of the evening trough FEV_1 95% CI was greater than the pre-defined non-inferiority margin of −100 mL, thus demonstrating non-inferiority of FF/VI to FP/SAL for the primary endpoint. In the intent-to-treat population, the least squares mean improvement in evening trough FEV_1 at Week 24 was greater for FF/VI than with fluticasone (123 mL, P<0.001) and for FP/SAL than with fluticasone (104 mL, P<0.001). Secondary: Baseline percentages of rescue-free 24-hour periods were comparable across the arms (range, 97.7 to 98.4%). The change from baseline in rescue-free 24-hour periods over 24 weeks was similar for FF/VI versus FP/SAL (1.2%; 95% CI, −0.5 to 3.0), while a 2.7% difference was observed for FF/VI versus fluticasone (95% CI, 0.9 to 4.4; P=0.002). The difference between FP/SAL and fluticasone was 1.4%. Baseline percentages of symptom-free 24-hour periods were comparable across the treatment arms (range 97.1 to 98.4%). The change from baseline in symptom-free 24-hour periods over 24 weeks was similar for FF/VI versus FP/SAL (1.2%; 95% CI, −0.7 to 3.1), while a 2.7% difference was observed for FF/VI versus fluticasone (95% CI, 0.8 to 4.5; P=0.004). The difference between FP/SAL and fluticasone was 1.5%. Baseline mean morning PEF values were similar across the treatment arms

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(range 407.4 to 414.4 L/min). The least squares mean change from baseline to 24 weeks in morning PEF was similar for FF/VI and FP/SAL, but improved with FF/VI versus fluticasone (21.5 L/min; 95% CI 17.4 to 25.6; P<0.001) and with FP/SAL versus fluticasone (16.3 L/min; 95% CI, 12.2 to 20.4; P<0.001). Baseline mean ACT scores were comparable across the treatment arms (range 23.4 to 23.6). At Week 24, the proportion of patients with an ACT score ≥ 20 was maintained in all treatment groups (92% FF/VI; 93% FP/SAL; 91% FP).
Lee et al.[60] (2021) CAPTAIN Fluticasone furoate-umeclidinium-vilanterol 100-31.25-25 µg once daily vs fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg once daily vs fluticasone furoate-umeclidinium-vilanterol 200-31.25-25 µg once	DB, MC, PG, RCT Patients ≥18 years of age with inadequately controlled asthma despite ICS/LABA, a documented health-care contact or a documented temporary change in asthma therapy for treatment of acute asthma symptoms in the year before screening, pre-bronchodilator FEV_1 between 30% and less than 85% of predicted normal value, and reversibility at screening	N=2,439 52 weeks	Primary: Change from baseline in clinic trough FEV_1 at week 24 Secondary: Annualized rate of moderate and/or severe asthma exacerbation	Primary: Addition of umeclidinium 62.5 µg to fluticasone furoate-vilanterol 100-25 µg and fluticasone furoate-vilanterol 200-25 µg resulted in a LSM change from baseline of 110 mL (95% CI, 66 to153) for fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg and of 92 mL (95% CI, 49 to 135) for fluticasone furoate-umeclidinium-vilanterol 200-62.5-25 µg in clinic trough FEV_1 at week 24. These increases were statistically significant, and therefore the primary endpoint was met. Improvements were also observed with the addition of umeclidinium 31.25 µg to both fluticasone furoate-vilanterol 100-25 µg (96 mL [95% CI, 52 to139]) and fluticasone furoate-vilanterol 200/25 µg (82 mL [95% CI, 39 to125]. Secondary: The number of moderate or severe exacerbations reported in the pooled fluticasone furoate-vilanterol treatment group was 379, in the fluticasone furoate-umeclidinium 31.25 µg-vilanterol pooled treatment group was 367, and in the fluticasone furoate-umeclidinium 62.5 µg-vilanterol pooled treatment group was 329. In the pooled analysis, addition of umeclidinium 62.5 µg to fluticasone furoate-vilanterol resulted in a 13% (95% CI, -5.2 to 28.1) reduction in the annualized rate of moderate and/or severe exacerbations (aRR=0.87 [0.72 to 1.05]; No reduction in the annualized rate of moderate and/or severe exacerbations was observed with the addition of umeclidinium 31.25 µg to fluticasone furoate-vilanterol. In prespecified unpooled analyses, there was a numerically lower annualized rate of moderate and/or severe exacerbations in the fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg group than in both the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs fluticasone furoate-umeclidinium-vilanterol 200-62.5-25 µg once daily vs fluticasone furoate-vilanterol 100-25 µg once daily vs fluticasone furoate-vilanterol 200-25 µg once daily				fluticasone furoate-umeclidinium-vilanterol 100-31.25-25 µg and fluticasone furoate-vilanterol 100-25 µg groups. Compared with fluticasone furoate-vilanterol 100-25 µg, the annualized rate of moderate and/or severe exacerbations was reduced by 21.8% (95% CI, -1.1 to 39.5) in the fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg group (aRR=0.78, 0.61 to 1.01) and 12.0% (-13.3 to 31.6) in the fluticasone furoate-umeclidinium-vilanterol 100-31.25-25 µg group (aRR=0.88, 0.68 to 1.13). By contrast, no additional reductions were observed when umeclidinium 62.5 µg or 31.25 µg was added to fluticasone furoate-vilanterol 200-25 µg.
Qaqundah et al.[61] (2006) Fluticasone propionate HFA 88 µg BID vs placebo	RCT Children 1 to <4 years of age with a history of symptomatic asthma and ≥2 episodes of increased asthma symptoms requiring medical attention/asthma treatment within the	N=359 12 weeks	Primary: Mean percent change from baseline to endpoint in 24-hour daily asthma symptom scores Secondary: Mean change from baseline to endpoint in daily	Primary: Fluticasone propionate group had a significantly greater mean percent (P=0.036) reduction in 24-hour daily asthma symptom scores vs placebo. Secondary: Fluticasone propionate group had significantly greater (P<0.05) reduction in nighttime asthma symptom scores over the treatment period vs placebo; mean change in 24-hour daily asthma symptom scores was also significantly increased in fluticasone propionate group. Fluticasone propionate group had improved daily SABA use, daytime symptom scores, and nighttime symptoms scores vs placebo; however, the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	year before screening		rescue SABA use; time to treatment failure; mean change in 24-hour daily asthma symptom scores; clinic morning PEF.	differences were not statistically significant. A total of 65 children (18%) were able to produce technically acceptable morning PEF measurements. At treatment week 12, mean change from baseline was 14.1 L/min in the fluticasone propionate group (n=34) vs 8.3 L/min for the placebo group (n=23). The number of children able to perform PEF measures was too low to allow meaningful comparisons between the treatment groups.
Nelson et al.[62] (1999) Fluticasone propionate 500 µg BID vs fluticasone propionate 1,000 µg BID vs placebo	DB, PC, PG, RCT Patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria who were receiving oral corticosteroid treatment over the preceding six months	N=111 16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose and mean change from baseline in maintenance dose of prednisone Secondary: Changes in FEV_1, patient-measured morning and evening PEF, patient-rated asthma symptoms and number of nighttime awakenings requiring albuterol	Primary: At 16 weeks, oral prednisone use was discontinued in 75 and 89% of patients treated with fluticasone propionate 500 or 1,000 µg BID, respectively, compared to 9% of placebo-treated patients. The mean maintenance dose of oral prednisone decreased significantly in both fluticasone propionate groups compared to the placebo group ($P<0.001$). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone propionate 500 µg BID group (8.37±3.84) and 1,000 µg BID group (24.21±5.67) compared to the placebo group (0.56±5.56; $P\leq0.05$ for all). Both morning and evening PEF improved in the fluticasone propionate 500 µg BID group (23+10 morning and 3±7 evening) and 1,000 µg group (67±12 morning and 48±10 evening) compared to the placebo group (-23±11 morning and -9±12 evening; $P\leq0.05$ for all). Asthma symptom scores improved in both the fluticasone propionate 500 µg BID (-0.26±0.08) and 1,000 µg BID groups (-0.47±0.13; $P\leq0.05$), while symptom scores worsened in the placebo group (0.26±0.12; $P\leq0.05$). Nighttime awakenings requiring albuterol decreased in both the fluticasone propionate 500 µg BID (-0.19±0.11) and 1,000 µg BID groups (-0.42±0.13), while nighttime awakenings increased in the placebo group (0.26±0.15; $P\leq0.05$ for all).
Fish et al.[63]	MC, PC, RCT	N=132	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Mometasone 400 to 800 µg BID vs placebo	Patients with severe, persistent, oral corticosteroid-dependent asthma	12 weeks, followed by 9 month OL phase	Percentage change in daily oral corticosteroid prednisone requirement Secondary: Spirometric measurements (FEV_1, FVC, FEF, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use and general and asthma-specific quality-of-life measures	Oral corticosteroid requirements were reduced by 46.0% in the mometasone 400 µg BID group and by 23.9% in the mometasone 800 µg BID group compared to the placebo group (164.4%; P<0.01). Oral corticosteroids were discontinued in 40, 37 and 0% of patients after 12 weeks and 71, 62 and 58% of patients at the end of the nine month OL phase in the mometasone 400 and 800 µg BID and placebo groups, respectively. Secondary: Nocturnal awakenings were reduced by 57 and 66% in the mometasone 400 and 800 µg BID groups, respectively, and increased by 62% in the placebo group (P<0.01). Daily rescue medication use was significantly reduced in the mometasone 400 µg BID group (P<0.01), but not in the mometasone 800 µg BID group compared to the placebo group. There were no statistically significant differences between the treatment groups with regard to all other secondary endpoints.
Schmier et al.[64] (2003) Mometasone 400 to 800 µg BID vs placebo	DB, MC, PC, RCT Patients with severe persistent asthma previously maintained on oral steroids	N=132 12 weeks, followed by a 9 month OL extension	Primary: Corticosteroid use, AQLQ-M Secondary: Not reported	Primary: Mometasone treated patients had a reduction in oral steroids requirement and a significant improvement in the SF-36 physical component summary score and the physical function subscale (P<0.05) compared with placebo. Mometasone treated patients also showed a significant improvement in each of the four subscales of the AQLQ-M (P<0.05). Secondary: Not reported
Krouse et al.[65](abstract)	DB, PC, RCT	N=20	Primary: Nocturnal decline	Primary: No significant differences were observed between groups with regard to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Mometasone 400 µg QPM vs placebo	Patients 18 to 60 years of age with mild to moderate asthma and a history of nocturnal asthma	14 days	in evening to morning FEV_1 values Secondary: Nocturnal decline in evening to morning PEFR values, polysomnographic indices of sleep, NRQLQ, SF-36 and AQLQ	nocturnal decline in FEV_1. Secondary: No significant differences were observed between groups with regard to polysomnographic indices of sleep, NRQLQ, SF-36 or AQLQ. A trend toward improvement in the activity scale of the AQLQ was observed in the mometasone group.
Price et al.[66] (2010) Mometasone 400 µg QPM vs mometasone 200 µg BID	MC, OL Patients 12 years of age and older with mild to moderate persistent asthma for at least one year	N=1,233 12 weeks	Primary: Adherence, measured by automatic dose counter Secondary: Self-reported adherence, physician's assessment of therapeutic response, HRQOL, healthcare resource utilization and days missed from work or school	Primary: Adherence, as measured by the automatic dose counter was significantly higher in the QPM group compared to the BID group (P<0.001). Secondary: Adherence, as measured by self-report was significantly higher in the QPM group compared to the BID group (P<0.001). No significant differences between groups were observed in physician's assessment of therapeutic response, HRQOL, healthcare resource utilization, or days missed from work or school (P≥0.08 for all).
Busse et al.[67] (1999) Beclomethasone HFA 100 µg/day vs	DB, MC, PG, RCT Asthmatic patients who had deteriorated in their asthma control following	N=323 6 weeks	Primary: Change from baseline in FEV_1 percent predicted Secondary: Percent change	Primary: For each treatment group, the FEV_1 percent predicted increased over the first four weeks of treatment and plateaued by week six. The change from baseline in FEV_1 percent predicted was greater with beclomethasone 800 µg/day HFA (-32.7%; P=0.049) compared to beclomethasone 400 µg/day HFA (-25.1%) and numerically, but not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
beclomethasone HFA 400 µg/day vs beclomethasone HFA 800 µg/day vs beclomethasone CFC 100 µg/day vs beclomethasone CFC 400 µg/day vs beclomethasone CFC 800 µg/day	discontinuation of ICS		from baseline in $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings and daily albuterol use	significantly greater (P=0.09) with beclomethasone CFC 800 µg/day (-31.3%) compared to beclomethasone CFC 400 µg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25\ to\ 75\%}$, FVC and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar among all treatment groups.
Papi et al.[68] (2007) Beclomethasone 250 µg BID and albuterol 100 µg as needed (regular beclomethasone) vs beclomethasone-albuterol 250-100 µg in a single	DB, DD, MC, PG, RCT Patients 18 to 65 years of age with asthma for ≥6 months, pre-bronchodilator FEV_1 ≥75% of predicted value, associated with either an increase in FEV_1 ≥12% of predicted value after	N=455 6 months	Primary: Mean rate of morning PEFR Secondary: Lung function, symptom scores, and number/ severity of exacerbations	Primary: The morning PEFR at six months was significantly higher among patients receiving as-needed combination therapy and in for patients receiving regular beclomethasone therapy compared to the use of as-needed albuterol therapy. The morning PEFR did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy. Secondary: The evening PEFR was significantly higher in the group receiving regular beclomethasone therapy, but not in the group receiving as-needed combination therapy compared to as-needed albuterol therapy. The pre bronchodilator FEV_1 and FVC were significantly higher after as-needed combination therapy, but not after regular beclomethasone therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaler as needed (as needed combination) vs beclomethasone-albuterol 250-100 µg BID in a single inhaler and albuterol 100 µg as needed (regular combination) vs albuterol 100 µg as needed (as needed albuterol)	inhalation of 200 µg of albuterol or a positive methacholine challenge			compared with as-needed albuterol therapy. These values did not differ significantly between patients receiving as-needed combination therapy and those receiving regular beclomethasone therapy or regular combination therapy. The FEV_1 and FVC increased significantly in the as-needed combination group and in the regular combination group, and evening PEFR increased significantly in the regular combination group. The evening PEFR and FEV_1 (percentage of the predicted value) increased significantly in the regular beclomethasone group. The group receiving as-needed combination therapy had fewer nocturnal awakenings, and the group receiving regular beclomethasone had less daily use of rescue medication compared to as-needed albuterol therapy. The percentage of symptom-free days was significantly higher in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy. The percentage of symptom-free days increased significantly in all groups, except the group receiving as-needed albuterol therapy, in which the number of nocturnal awakenings increased significantly. The regular beclomethasone group had fewer daytime asthma symptoms. A total of 237 exacerbations occurred during the study, 38 in patients receiving as-needed combination therapy, 83 in those receiving as-needed albuterol therapy, 33 in those receiving regular beclomethasone therapy, and 83 in those receiving regular combination therapy. The mean number of exacerbations per patient per year was lower in the as-needed combination group (0.74) and in the regular beclomethasone group (0.71) than in the as-needed albuterol group (1.63; $P<0.001$) and in the regular combination group (1.76; $P<0.001$). The percentage of patients with at least one exacerbation was not significantly different in the group receiving as-needed combination therapy (4.92%) and the group receiving regular beclomethasone therapy (5.66%; $P=0.802$) or the group receiving regular combination therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(10.09%; P=0.133). The percentage of patients with at least one exacerbation was significantly lower both in the group receiving as-needed combination therapy and in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (17.80%) (P=0.002 and P=0.005, respectively). The time to first exacerbation differed significantly between groups, with the shortest time to first exacerbation in the as-needed albuterol group (P=0.003 by the log-rank test).
Sharek et al.[69] (2000) Beclomethasone 328 to 400 µg/day vs fluticasone propionate 200 µg/day	MA 1966 to 1998, DB, RCT studies that evaluated linear growth in children six to 16 years of age with asthma and concomitant ICS therapy	N=855 (5 studies)	Primary: Linear growth velocity in cm/year Secondary: Not reported	Primary: There was a significant decrease in linear growth in children using beclomethasone for mild-to-moderate asthma. The WMD between 231 patients using beclomethasone compared to 209 patients using a non-steroid medication was -1.51 cm/year (95% CI, -1.15 to -1.87). For the fluticasone propionate study the mean difference between 96 children treated with fluticasone propionate and 87 patients treated with placebo was -0.43 cm/year (95% CI, -0.01 to -0.85; P value not reported). Secondary: Not reported
van Aalderen et al.[70] (2007) Beclomethasone 200 µg/day via HFA MDI vs fluticasone propionate 200 µg/day via CFC MDI During weeks seven to 12 and 13	AC, DB, DD, PG, RCT Patients five to 12 years of age with asthma for at least three months, a PEF ≥60% of predicted normal, and currently using a SABA on an as-needed basis	N=139 18 weeks	Primary: Morning PEF percent predicted Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent predicted, symptom-free days, nights without sleep disturbances, use of a β_2-agonist, asthma control, quality of life and	Primary: The mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.9 (90% CI, -4.9 to 1.0; P value not reported). Secondary: The mean change from baseline in evening PEF percent predicted was 5.9% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.5 (90% CI, -4.6 to 1.6; P=0.415). The mean change from baseline in FEV_1 percent predicted was 3.0% in the beclomethasone group and 0.6% in the fluticasone propionate group. The treatment difference was 1.6 (P=0.335). The mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone propionate group. The

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to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control. Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.			adverse events	treatment difference was 4.6 (P=0.084). The percent change from baseline in symptom-free days was 35.2% in both treatment groups (P=0.897). The percent change in nights without sleep disturbances was 17.5 and 20.8% in the beclomethasone and fluticasone propionate groups, respectively (P=0.561). The mean use of a β_2-agonist decreased from 1.59 to 0.73 puffs/day in the beclomethasone group, and from 1.40 to 0.69 puffs/day in the fluticasone propionate group (P=0.505). At six weeks, 36% of patients in the beclomethasone group and 42% in the fluticasone propionate group had good asthma control and were able to step down in their respective doses to 100 µg/day. At 12 weeks, another step down therapy to 50 µg/day was possible in 66 and 61% of the patients in the beclomethasone and fluticasone propionate groups, respectively. The proportion of patients with a clinically significant improvement in asthma quality of life was similar in both groups (P=0.369). There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone propionate (49%) groups.
Berkowitz et al.[71] (1998) Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs	AC, DB, DD, PC, RCT Patients 18 to 65 years of age with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, PEFR and FVC	Primary: For both active treatment groups, patients experienced statistically significant increases from baseline in FEV_1 compared to the placebo group at all time points (P<0.05 for all). Over the course of the study, the FEV_1 was significantly increased by 10.3% in the beclomethasone group and by 11.2% in the triamcinolone group compared to the placebo group ($P \leq 0.05$ for both). Secondary: The mean increases in $FEF_{25\ to\ 75\%}$ FVC and PEFR were among the beclomethasone and triamcinolone treatment groups. All results were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				numerically and statistically significant compared to the placebo group (P<0.05).
Bronsky et al.[72] (1998) Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs placebo	AC, DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on an ICS	N=328 56 days	Primary: Mean changes from baseline in FEV_1 Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC	Primary: The mean change from baseline in FEV_1 for both active treatments was significantly greater compared to placebo (0.27 and 0.16 vs -0.10 L for beclomethasone and triamcinolone compared to placebo; P≤0.01 for both). Secondary: At each visit, the mean improvements in total symptom severity scores were significantly greater in the beclomethasone group compared to the triamcinolone group (P=0.028) and at endpoint in both active treatment groups compared to the placebo group (-1.37, -0.58, and 0.83; P<0.001 for all). The mean average daily use of albuterol calculated weekly was lowest in the beclomethasone group (2.86) followed by the triamcinolone group (3.61) and the placebo group (4.43; P values not reported). Nighttime awakenings were not significantly different among the treatment groups. The mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC demonstrated both active treatment groups to be more effective compared to the placebo group, and beclomethasone being more effective than triamcinolone throughout the study.
Ferguson et al.[73] (2007) Budesonide 200 µg BID via DPI vs fluticasone propionate 100 µg BID via DPI	AC, DB, DD, MC, PG, RCT Children six to nine years of age with persistent asthma for at least six months, and an FEV ≥60% predicted, height between the 5th and 95th percentiles for the	N=400 12 months	Primary: Growth velocity Secondary: PEFR, FEV_1, exacerbations, symptoms-free days and nights, salbutamol-free nights and adverse events	Primary: Mean growth velocity from baseline was 5.5 cm/year in the fluticasone propionate group and 4.6 cm/year in the budesonide group. This difference of 0.9 cm/year was statistically significant (P<0.001). The difference in growth velocities increased over the 12 months. The majority of patients in the fluticasone propionate group grew 5.0 to 7.0 cm/year whereas patients in the budesonide group grew 3.0 to 5.0 cm/year. Secondary: Change in morning PEFR was 29.7 and 26.2 L/minute for the fluticasone propionate and budesonide groups, respectively (P=0.460).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	patients' age and run-in growth velocity between the 20th and 95th percentiles			Change in FEV_1 was 0.19 and 0.25 L for the fluticasone propionate and budesonide groups, respectively (P=0.154). The proportions of patients with no exacerbations were 75 and 68% in the fluticasone propionate and budesonide groups, respectively (P=0.131). The proportion of patients who were 100% symptom-free was 49 and 48% in the fluticasone propionate and budesonide groups respectively (P=0.799). The proportion of patients who had 100% symptom-free nights was 50 and 58% in the fluticasone propionate and budesonide groups respectively (P=0.232). The proportion of patients who had 100% salbutamol-free nights was 57 and 52% in the fluticasone propionate and budesonide groups respectively (P=0.180). Adverse events were reported in 81 and 71% of the fluticasone propionate and budesonide groups, respectively. Less than 3% of these events were considered to be treatment-related.
Weiss et al.[74] (2004) Budesonide 200 to 1,600 µg/day vs triamcinolone 1,200 to 1,600 µg/day	AC, OL, RCT Adult patients with persistent asthma enrolled in 25 United States health plans	N=945 52 weeks	Primary: Mean change from baseline in symptom-free days Secondary: Changes from baseline in number episode-free days, FEV_1, FVC, asthma symptom scores, breakthrough bronchodilator use and HRQOL	Primary: Increases from baseline in mean estimated symptom- and episode-free days occurred in both groups by month one and were maintained throughout the treatment period. These increases were consistently greater with budesonide than with triamcinolone (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; P<0.001 for both). Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and episode-free days over the 52-week treatment period were significantly greater in the budesonide group compared to the triamcinolone group (P<0.001). The mean FEV_1 and FVC improved from baseline in both groups. Patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				receiving budesonide experienced a greater improvement in FEV_1 compared to patients receiving triamcinolone (0.35 vs 0.25 L; P=0.005). The difference between the two groups in FVC was not statistically significant. The mean daytime and nighttime asthma symptom scores improved from baseline in both groups. Improvements were significantly greater in patients receiving budesonide at month 12 compared to patients receiving triamcinolone (P=0.001 and P<0.001, respectively). The mean amount of breakthrough bronchodilator use decreased from 4.42 to 2.58 puffs/week in the budesonide group (95% CI, -2.17 to -1.58) and from 4.56 to 3.68 puffs/week in the triamcinolone group (95% CI, -1.36 to -0.52; P<0.001). Patients in both treatment groups reported significant improvements from baseline over the course of the study in overall quality of life and the individual domains of the HRQOL questionnaire. Compared to the triamcinolone group, the budesonide group reported significantly greater improvements in SF-36 general health scores at weeks 26 and 52 (P<0.05 and P=0.001, respectively).
Niphadkar et al.[75] (2005) Ciclesonide 160 µg QAM or QPM vs budesonide 200 µg BID	DB, MC, OL, RCT Patients 18 to 69 years of age with persistent asthma for ≥6 months that was maintained on a constant dose of ICS and FEV_1 ≥70% predicted	N=405 12 weeks	Primary: Change in FEV_1 Secondary: FVC, PEF, asthma symptom scores, rescue medication use	Primary: Ciclesonide and budesonide maintained FEV_1 as compared with baseline. Ciclesonide was non-inferior to budesonide with regard to maintenance of FEV_1 (PP analysis: 95% CI, -0.075 to 0.095 for ciclesonide 160 µg QAM vs budesonide, 95% CI, -0.051 to 0.123 for ciclesonide 160 µg QPM vs budesonide). No significant differences were found among the three treatment groups with regard to the change in FEV_1 at the end of treatment. Similar results were obtained in the ITT analysis. Secondary: Ciclesonide was found to be non-inferior to budesonide with regard to maintenance of FVC in all treatment groups, and no significant differences were found among the groups. The mean change in morning PEF was 8.0 L/min in the ciclesonide 160 µg PM group, compared with -5.7 L/min in the ciclesonide 160 µg AM group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and -1.3 L/min in the budesonide (all groups; P=NS). Evening PEF was maintained in all treatment groups. No significant differences were found among the three treatment groups for the secondary endpoints FVC, PEF by spirometry, and morning and evening PEF by diary. Ciclesonide 160 µg QAM, ciclesonide 160 µg QPM, and budesonide maintained asthma symptom scores, and no significant differences were found between the treatment groups. The percentages of days that were free of asthma symptoms and need for rescue medication were 89, 91, and 93% for patients taking ciclesonide 160 µg QAM, ciclesonide 160 µg QPM, and budesonide, respectively, with no differences between the treatment groups. The percentage of days that were free of nocturnal awakening was 100% in all treatment groups. Rescue medication use, days with control of asthma symptoms, and days without PEF fluctuation, were maintained vs baseline, and no significant differences were found between the treatment groups. Both treatments were well tolerated.
von Berg et al.[76] (2007) Ciclesonide 160 µg QPM vs budesonide 400 µg QPM	AC, DB, DD, MC, PG, RCT Patients six to 11 years of age with persistent asthma for at least six months	N=621 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change in morning PEF, asthma symptom score, rescue medication utilization, percentage of days without asthma symptoms and without need for rescue medication,	Primary: Significant increases from baseline in FEV_1 occurred in both the ciclesonide (0.232 L; P<0.0001) and budesonide (0.250 L; P<0.0001) treatment groups. Ciclesonide proved to be non-inferior to budesonide with no significant differences between treatment groups (P=0.8158). Secondary: Both treatment groups experienced a statistically significant increase in morning PEF compared to baseline (ciclesonide, 22.5 L/minute; P<0.0001, budesonide, 26.3 L/minute; P<0.0001). There were no significant differences between treatment groups (P=0.8531). Both treatment groups experienced a statistically significant improvement in asthma symptom score (zero to five scale) after 12 weeks of treatment (ciclesonide, -1.21; P<0.0001, budesonide, -1.21; P<0.0001). There were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			percentage of patients with asthma exacerbations, PAQLQS and PACQLQ score, adverse events, body height increase at week 12, and change in 24-hour urinary cortisol	no significant differences between treatment groups (P=0.8379). Both treatment groups experienced a statistically significant reduction in the need for rescue medication (puffs/day) after 12 weeks of treatment compared to baseline (ciclesonide, -1.58; P<0.0001, budesonide, -1.64; P<0.0001). There were no significant differences between treatment groups (P=0.8593). The percentage of days without asthma symptoms and without need for rescue medication was 73% in the ciclesonide treatment group, and 70% in the budesonide treatment group (P value not reported). The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide treatment group and 1.0% in the budesonide treatment group (P value not reported). Both treatment groups experienced a statistically significant improvement in overall PAQLQS (one to seven scale) and PACQLQ scores compared to baseline (0.69, 0.88 and 0.70, 0.96 for the ciclesonide and budesonide treatment groups respectively (P<0.0001 for all). The percentage of patients who experienced treatment-emergent adverse events was 38% among both treatment groups. The most common adverse events that occurred in at least 5% of patients in the ciclesonide and budesonide treatment groups, respectively, were pharyngitis (5.9 vs 3.8%), nasopharyngitis (4.1 vs 5.4%), upper respiratory tract infection (3.6 vs 6.3%) and oropharyngeal infection (0.2 vs 1.5%). At week 12 the body height increased by 1.18 cm in the ciclesonide treatment group and by 0.70 cm in the budesonide treatment group (P<0.0001 for both). The increase in height was significantly greater in the ciclesonide treatment group than in the budesonide treatment group (P=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine) (ciclesonide, -2.17; P<0.0001, budesonide, -5.16; P<0.0001). The difference between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment groups was significant (P<0.0001).
Boulet et al.[77] (2006) Ciclesonide 320 µg QD vs budesonide 320 µg QD	DB, MC, RCT Patients 12 to 75 years of age with persistent asthma for ≥6 months, FEV_1 65 to 95% of predicted value, receiving treatment with budesonide 320 to 640 µg, fluticasone propionate 175 to -440 µg/day or equivalent. patients entering the treatment period had to fulfill inclusion criteria and demonstrate improvement in FEV_1 during the pretreatment period of either ≥7% or 0.15 L following the increase in their daily ICS dose from budesonide 320 to 640 mg (or the equivalent) to budesonide 1,280 mg.	N=359 12 weeks	Primary: Change in FEV_1, FVC, PEF, asthma symptom scores, rescue medication use Secondary: Not reported	Primary: During the pretreatment period with budesonide 1,280 mg daily, mean FEV_1 levels increased by 0.352 L for the ciclesonide group and 0.319 L for the budesonide group. After patients were randomized to either ciclesonide 320 mg or budesonide 320 mg QD, FEV_1 decreased by 0.18 and 0.23 L, respectively, over 12 weeks of treatment (P<0.0001; PP analysis). Ciclesonide was non-inferior to budesonide with regard to maintenance of FEV_1 (95% CI, -0.015 to 0.121 for ciclesonide vs budesonide; PP analysis). Similar results were obtained by ITT analysis. There were no significant differences between the two treatment groups with regard to change in FEV_1 at the end of treatment. Mean FVC levels decreased in both treatment groups, the decrease in ciclesonide patients (0.12 L; P<0.0001, within-treatment comparison) compared with that in budesonide patients (0.21 L; P<0.0001, within-treatment comparison) was significantly less (95% CI, 0.02 to 0.147; P=0.011 for ciclesonide vs budesonide; ITT analysis). Similar results were obtained after PP analysis. There was no significant difference in morning PEF between the treatment groups. Mean evening PEF levels did not significantly change with ciclesonide or budesonide. There were no significant differences between the two treatment groups in median asthma symptom score sums, night scores, and daytime scores over the treatment period. The percentage of asthma symptom-free days was 43.6% in the ciclesonide group compared with 25.8% in the budesonide group. Patients treated with ciclesonide experienced a significant reduction in the median rescue medication use over the course of treatment (P=0.009) compared to no change in those treated with budesonide (P=0.626). There was a significant difference between treatment groups in median rescue medication use (P=0.026). The median percentage of rescue medication-free days was similar in both groups (57.5 vs 53.6% for ciclesonide and budesonide group, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between treatment groups with regard to lack of efficacy, physician assessments, or patient self-assessments. A total 52% of patients in the budesonide group and 42% of patients in the ciclesonide group experienced an adverse event. Secondary: Not reported
Ukena et al.[78] (2007) Ciclesonide 320 µg QPM vs budesonide 400 µg QPM	DB, MC, PG, RCT Patients 12 to 75 years of age with asthma for ≥6 months, FEV_1 50 to 90%	N=399 12 weeks	Primary: Change in FEV_1 Secondary: FVC, PEF, asthma symptom scores, use of rescue medication	Primary: After 12 weeks, FEV_1 increased by 416 mL in the ciclesonide group and by 321 mL in the budesonide group (P<0.0001 vs baseline for both). Ciclesonide was significantly more effective than budesonide demonstrated (P=0.019). Secondary: Patients experienced significant improvements in FVC and PEF with ciclesonide and budesonide (P<0.0001 vs baseline for both). Patients treated with ciclesonide achieved a significantly greater increase in FVC (P=0.034) and PEF by spirometry (P=0.019) compared with budesonide. Significant increases in asthma symptom scores and decreases in use of rescue medication were observed with ciclesonide and budesonide. Ciclesonide and budesonide significantly improved asthma symptom scores from baseline (both P<0.0001). There was no significant difference between the treatment groups (P=0.863). Ciclesonide and budesonide improved rescue medication use compared to baseline (P<0.0001). There was no significant difference between the treatment groups. Ciclesonide treatment achieved a significant improvement in morning PEF by day two (P=0.039 vs baseline) compared with day seven for budesonide (P=0.047 vs baseline). Adverse events occurred with a similar incidence in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vermeulen et al.[79] (2007) Ciclesonide 320 µg QPM vs budesonide 800 µg QPM	AC, DB, DD, MC, PG, RCT Patients 12 to 17 years of age with severe asthma for six months with an FEV_1 50 to <80% who were not controlled with budesonide 400 µg/day for at least four weeks prior to study	N=403 12 weeks	Primary: Change from baseline in evening pre-dose FEV_1, percentage of days without asthma symptoms and without use of rescue medication Secondary: Change from baseline in FEV_1, percentage of patients experiencing an asthma exacerbation, morning PEF, asthma symptom score, albuterol utilization, PAQLQS score and adverse events	Primary: At 12 weeks, significant increases from baseline in FEV_1 were reported in both the ciclesonide (0.505 L; P<0.0001) and budesonide (0.536 L; P<0.0001) treatment groups. There were no significant differences between treatment groups (P=0.076). The percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (P value not reported). Secondary: FEV_1 percent predicted increased in the ciclesonide group from 73.1 percent at baseline to 89.4% at the end of the study. In the budesonide group FEV_1 percent predicted was 73.0% at baseline and 90.7% at the end of the study. There was no significant difference between the two study groups (P value not reported). The change from baseline in FVC was significant in both the ciclesonide and budesonide treatment groups (0.433 and 0.472 L, respectively). The difference between the treatment groups was not significant (P=0.080). Asthma exacerbations were reported in 2.6% of patients in the ciclesonide group and 1.5% of patients in the budesonide group. There was no significant difference between the two treatment groups (P value not reported). Morning PEF increased from baseline by 8.0 L/minute in the ciclesonide group (P=0.0424) and 4.9 L/minute in the budesonide group, which was not statistically significant (P value not reported). Asthma symptom scores (zero to five scale) were significantly improved from baseline in both the ciclesonide and budesonide treatment groups (-0.07 and -0.14, respectively; P<0.05 for both). There were no significant differences between treatment groups (P value not reported). The median use of rescue medication was reduced to zero puffs/day in both the ciclesonide (P<0.0001) and budesonide groups (P=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall PAQLQS scores (one to seven scale) were improved in both treatment groups (ciclesonide, 0.19; P=0.0001 and budesonide, 0.18; P=0.0056). The percentage of patients who experienced treatment emergent adverse events was comparable among the ciclesonide and budesonide treatment groups (26.5 vs 18.3%, respectively). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (5.9 vs 3.8%, respectively).
Hansel et al.[80] (2006) Ciclesonide 80 µg QD vs ciclesonide 320 µg QD vs budesonide 200 µg BID	DB, MC, OL, RCT Patients 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: Change in FEV_1 Secondary: Changes from baseline in morning PEF, asthma symptom scores, and rescue medication use	Primary: Significant increases from baseline in FEV_1 were achieved in all three groups (all; P<0.001). Ciclesonide was found to be non-inferior to budesonide with regard to mean changes from baseline in FEV_1 (ITT, 97.5% CI, -0.192 to 0.015 for ciclesonide 80 µg vs budesonide; 97.5% CI, -0.200 to 0.001for ciclesonide 320 µg vs budesonide). Similar findings were seen in the PP population. There was no significant difference between the two ciclesonide groups. Secondary: Morning PEF was improved significantly in the ciclesonide 80 and 320 µg groups, as well as the budesonide group (all; P<0.008). Ciclesonide was found to be non-inferior to budesonide. No significant differences in morning PEF were found between the two ciclesonide groups. Significant improvements were found in median daily asthma symptom scores in all three treatment groups (all; P<0.001). Significant improvements were found in median daytime and nighttime asthma symptom scores in all three groups (all; P<0.001). Comparisons between treatments for daily, daytime, and nighttime asthma symptom scores did not demonstrate any significant differences throughout the study. Overall, the percentages of patients without any asthma symptoms (score, 0) increased from -20 to -40% after three days of treatment; these percentages were similar across all three treatment groups throughout the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study. The onset of effect for ciclesonide and budesonide, based on asthma symptom scores, occurred during the first week of treatment. However, in smokers treated with budesonide 200 µg BID (four patients), the mean onset of action was 4 weeks, whereas in smokers treated with ciclesonide 80 µg QD (23 patients) or 320 µg QD (15 patients), onset was within one week. There were significant decreases in rescue medication use in all three groups by day one of treatment (all; P<0.001). These decreases remained significant throughout the study in all three treatment groups (all; P<0.001). AEs were reported in 36.8% of patients receiving ciclesonide 80 µg QD, 80 (40.8%) patients receiving ciclesonide 320 µg QD, and 60 (33.9%) patients receiving budesonide 200 µg BID.
Buhl et al.[81] (2006) Ciclesonide 160 µg QD vs fluticasone propionate 88 µg BID	DB, MC, RCT Patients 12 to 75 years of age with asthma for ≥6 months, FEV_1 50 to 90% predicted after rescue medication was withheld for at least 4 hours, a decrease in FEV_1 ≥10% after ICS withdrawal, reversibility of FEV_1 ≥15% after inhaling 200 to 400 µg of salbutamol or have shown a diurnal PEF fluctuation ≥15%	N=529 12 weeks	Primary: Changes in FEV_1, FVC, PEF, $FEF_{25-75\%}$, asthma symptom scores, rescue mediation use Secondary: Not reported	Primary: Ciclesonide produced similar improvements in FEV_1 as fluticasone propionate (0.489 and 0.499 L for ciclesonide and fluticasone propionate, respectively; P=0.801; ITT). Similar improvements in FEV_1 were observed in the PP analysis (0.506 and 0.536 L for ciclesonide and fluticasone propionate, respectively; P=0.477). FVC and morning PEF increased to a similar extent in both treatment groups and there were no differences for these parameters between the groups (P=0.468 and P=0.582, respectively; ITT). Evening PEF values significantly improved over the 12 weeks following treatment with ciclesonide and fluticasone propionate. $FEF_{25-75\%}$ increased in both the ciclesonide and fluticasone propionate treatment groups by 0.519 and 0.601 L/s, respectively (P<0.0001 for both), and no significant differences were observed between treatment groups (P=0.264). PP analysis of all lung function variables revealed comparable results with the ITT analysis. There were no significant differences between asthma symptom scores in the ciclesonide and fluticasone propionate groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Ciclesonide and fluticasone propionate also significantly reduced rescue medication use with no significant differences between the groups. There was no significant difference between ciclesonide and fluticasone propionate with regards to rescue medication-free days, asthma symptom-free days, and nights without awakenings due to asthma. A total of 270 treatment-emergent AEs were experienced by 186 of the 529 patients (36% of patients in the ciclesonide group and 34% of patients in the fluticasone propionate group). Secondary: Not reported
Boulet et al.[82] (2007) Ciclesonide 320 µg QPM vs fluticasone propionate 200 µg BID	MC, OL, RCT Patients 12 to 75 years of age with moderate asthma for ≥6 months and FEV_1 60 to 80% of predicted. Patients had to have been on a constant dose and type of asthma medication (except rescue medication) during the 4 weeks prior to the run-in period.	N=474 12 weeks	Primary: Change in FEV_1, FVC, PEF, FEV_1% predicted, SVC, asthma symptom scores, rescue medication use, asthma control days, exacerbations, HRQOL Secondary: Not reported	Primary: FEV_1 increased significantly from baseline with ciclesonide and fluticasone propionate in the ITT and PP analyses (all P<0.0001). Treatment difference was -31 mL (95% CI, -121 to 59) in the PP analysis, demonstrating non-inferiority of ciclesonide. FVC improved significantly with both treatments with ciclesonide showing a similar effect to fluticasone propionate (-0.034; 95% CI, -0.134 to 0.066 in the PP population and -0.017; 95% CI, -0.105 to 0.070 in the ITT population). A significant increase in morning PEF was seen in the ciclesonide-treated group (ITT and PP; both P<0.050) and a significant decrease in evening PEF was seen in the fluticasone propionate -treated group (ITT population only; P=0.020). Non-inferiority was seen for ciclesonide in morning and evening PEF for both the ITT and PP populations. FEV_1% predicted and SVC improved significantly with both treatments in both populations. There were no significant between-treatment differences in any of these lung function parameters. In the ITT population, daytime and total median asthma symptom scores were reduced in the ciclesonide group by 0.25 (P<0.0001) and 0.29

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.0001), and in the fluticasone propionate group by 0.29 (P<0.0001) and 0.29 (P<0.0001), respectively. The median values for nighttime scores were 0 at baseline and end of study. The PP analysis yielded similar results. There were no significant differences in asthma symptom scores between the treatment groups. In the ITT population, the use of rescue medication decreased by 0.29 puffs/day (P<0.0001) in both treatment groups and there was no significant difference between treatments. The percentage of days with asthma control was achieved at similar rates in the two groups (85 and 84% in the ciclesonide and fluticasone propionate groups, respectively, in both the ITT and PP analyses). Asthma exacerbations were recorded in 1.3% of patients in the ciclesonide group and 2.1% of patients in the fluticasone propionate group (ITT). The mean AQLQ(S) overall score increased from 5.85 at baseline to 6.14 (P<0.0001) in the ciclesonide group and from 5.85 to 5.96 (P=0.030) in the fluticasone propionate group. The improvement with ciclesonide was significantly greater than with fluticasone propionate (P=0.005). Both ciclesonide and fluticasone propionate produced significant increases in all of the individual AQLQ(S) domain scores. Non-inferiority of ciclesonide to fluticasone propionate was seen in all domain scores (all P<0.0001) in the PP and ITT analyses. The improvement in the scores for the domains of 'activities' and 'symptoms' was significantly greater with ciclesonide vs fluticasone propionate (P<0.01). The overall frequency of adverse events was similar in the two treatment groups (36.1% in the ciclesonide group and 39.3% in the fluticasone propionate group).
Magnussen et al.[83] (2007) Ciclesonide 80 µg QPM	DB, PG, RCT Patients 12 to 75 years of age with persistent asthma for ≥6 months	N=808 12 weeks	Primary: Change in FEV_1 and change in nighttime asthma symptoms score	Primary: Ciclesonide 80 µg, ciclesonide 160 µg and fluticasone propionate achieved similar improvements in FEV_1 (P<0.0001 for all groups and time points vs baseline; ITT). PP analysis revealed similar results. Both doses of ciclesonide were found to be non-inferior to fluticasone propionate and led to similar improvements in FEV_1 from baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ciclesonide 160 µg QPM vs fluticasone propionate 88 µg BID			Secondary: PEF, FVC, asthma symptoms, rescue medication use, and days with asthma control	Non-inferiority of both ciclesonide 80 and 160 µg vs fluticasone propionate was achieved for PEF and FVC, as well as evening PEF. For morning PEF, the within-treatment improvements were statistically significant for all three treatment groups (P<0.0001). Non-inferiority was demonstrated for ciclesonide 160 µg vs fluticasone propionate, but not for ciclesonide 80 µg. Treatment with ciclesonide 80 µg, ciclesonide 160 µg and fluticasone propionate led to significant decreases in median asthma symptom scores (P<0.0001 vs baseline). Nighttime asthma symptom score significantly improved for all treatment groups, as well as daytime asthma symptom scores (P<0.0001 vs baseline). There were no significant differences among groups for asthma symptom scores. Similar results were obtained in the PP analysis. All three treatment groups significantly reduced rescue medication use (all P<0.0001 vs baseline), with no significant differences among treatment groups. The percentage of days with asthma control was similar in all treatment groups with no significant differences between groups. Only two patients in each of the ciclesonide 80 and 160 µg groups and one patient in the fluticasone propionate group experienced an asthma exacerbation that required treatment with oral steroids. A total of 25% of patients in the ciclesonide 80 µg group, 24% of patients in the ciclesonide 160 µg group and 27% of patients in the fluticasone propionate group experienced AEs.
Pedersen et al.[84] (2009) Ciclesonide 80 µg QD vs	DB, PG, RCT Patients 6 to 11 years of age with persistent asthma for ≥6 months, FEV_1 50 to 90% of	N=744 12 weeks	Primary: Change in FEV_1, PEF, exacerbations, asthma symptom scores, rescue medication use,	Primary: FEV_1 increased significantly in all treatment groups (P<0.0001). Non-inferiority was demonstrated for ciclesonide 160 µg vs fluticasone propionate (95% CI, -0.079 to 0.027; P=0.0030, whereas ciclesonide 80 µg was not shown to be non-inferior to fluticasone propionate. Morning PEF increased significantly in all treatment groups (all

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ciclesonide 160 µg QD vs fluticasone propionate 88 µg BID	predicted and FEV_1 reversibility of ≥12% predicted after salbutamol 200 to 400 µg		quality of life Secondary: Not reported	P<0.0001). Both ciclesonide doses were non-inferior to fluticasone propionate (P<0.0063 for both doses). Asthma exacerbations occurred in 7.1% of patients receiving ciclesonide 80 µg, 2.9% of patients receiving ciclesonide 160 µg, and 2.0% of patients receiving fluticasone propionate. The difference between the higher-dose treatments was not statistically significant, but both these treatments were significantly superior to ciclesonide with respect to time to onset of first exacerbation (P<0.021). All three treatments significantly decreased asthma symptom score sums and need for rescue medication (all P<0.0001). Between-treatment analyses confirmed non-inferiority of both ciclesonide groups to fluticasone propionate for asthma symptom score sums (P>0.5713). No significant differences were found between treatment groups for asthma symptom score sums and rescue medication use. The percentage of asthma symptom-free days, rescue medication- free days and nocturnal awakening-free days did not differ significantly between the treatment groups. Quality of life significantly improved for overall scores and all sub-categories of the questionnaires in all treatment groups (P<0.0001 for all). Between-treatment analyses for the overall PACQLQ and PAQLQ scores confirmed non-inferiority of ciclesonide 80 µg and ciclesonide 160 µg to fluticasone propionate (P<0.0001 for all). The percentage of patients experiencing AEs was comparable across all treatment groups (ciclesonide 80 µg, 46.4%; ciclesonide 160 µg, 41.7%; fluticasone propionate 176 µg, 47.6%).
Bateman et al.[85] (2008) Ciclesonide 160 µg, 2 inhalations BID	MC, MG, OL, RCT Patients 12 to 75 years of age with ≥6 month history of asthma, FEV_1 ≥80% of predicted,	N=528 6 months	Primary: Change in FEV_1 and drop-out rate due to asthma exacerbation Secondary:	Primary: FEV_1 was maintained from baseline to study end in both groups (mean increase, ciclesonide 11 mL, fluticasone propionate 24 mL; ITT analysis). The LS mean of the mean for the treatment difference was -13 (95% CI, -70 to 44) in the ITT analysis and -27 (95% CI, -93 to 40) in the PP analysis, demonstrating non-inferiority of ciclesonide to fluticasone propionate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate 110 µg, 3 inhalations BID Patients using LABAs, oral β_2-agonists, theophylline, leukotriene antagonists or lipoxygenase inhibitors could continue treatment provided the dose was kept constant throughout the trial.	reversibility of FEV_1 ≥12% after 200 to 400 µg salbutamol, and ≥1 day without asthma symptoms during the last 7 days; patients were receiving fluticasone propionate 500 to 1,000 µg/day		Morning and evening PEF; asthma symptom scores; use of rescue medication; percentage of days free from asthma symptoms, rescue medication and nocturnal awakenings; percentage of days with asthma control; and AQLQ(S)	Six patients in the ciclesonide group and seven in the fluticasone propionate group in the ITT analysis experienced an asthma exacerbation that required treatment with oral corticosteroids. Similar findings were seen in the PP data set (ITT: 95% CI, -0.031 to 0.028; PP: 95% CI, -0.016 to 0.043). Secondary: Both treatments significantly decreased asthma symptom score sum (ITT and PP analyses; all P<0.0001) and rescue medication use (ITT and PP analyses; all P<0.05). The treatment differences between ciclesonide and fluticasone propionate were not statistically significant for any of the asthma symptom scores or rescue medication use. Median values for percentages of symptom-free days, rescue-medication-free days and nocturnal-awakening-free days did not differ significantly between the two treatment groups. The percentage of days with asthma control was 74.1% in the ciclesonide group and 73.2% in the fluticasone propionate group. There was no significant difference between the treatment groups. There were significant improvements in HRQOL (HRQoL) in the two treatment groups for the overall AQLQ(S) score, as well as for all domain scores (ITT and PP analyses; all P<0.05). The frequency of AEs was comparable in both treatment groups.
Newhouse et al.[86] (2000) Flunisolide 750 µg BID (administered via AeroChamber®) vs	AC, MC, PG, RCT Patients with moderate asthma (FEV_1 40 to 85% of predicted)	N=176 6 weeks	Primary: Change from baseline in pre bronchodilator FEV_1 and albuterol usage Secondary: Changes in PEF, asthma scores and	Primary: There were no statistically significant differences between the two groups in the changes in FEV_1 during the six week treatment period (difference of -0.031 L in percent predicted favoring flunisolide; P=0.544). There were no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide; P=0.333). Secondary: There were no statistically significant differences between the two groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide 600 µg BID (administered via Turbuhaler®)			nocturnal awakenings	in the changes in PEF, asthma symptoms scores or nocturnal awakenings during the treatment period.
Berend et al.[87] (2001) Fluticasone propionate (at ~50% of the ICS dose during the run-in phase) vs beclomethasone or budesonide (at the same dose used during the run-in phase)	MC, OL, PG, RCT Patients 18 years of age or older with a history of severe asthma, currently receiving at least 1,750 µg/day of inhaled beclomethasone or budesonide	N=133 6 months	Primary: Changes from baseline in morning PEF and FEV_1 Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations and quality of life	Primary: Patients in the fluticasone propionate group experienced a significant improvement in morning PEF compared to patients continuing the same dose of their ICS (adjusted difference between two groups, 26±32 L/minute; 95% CI, 8 to 45; P=0.006). The changes from baseline in FEV_1 measured at clinic visits paralleled those values of the morning PEF (1.87±0.70 L with fluticasone propionate and 2.03±0.86 L with beclomethasone/budesonide; P values not reported). Secondary: Serum osteocalcin levels increased significantly in the fluticasone propionate group (adjusted mean [SD], 2.6 [4.0] µg/L; 95% CI, 0.2 to 4.9; P=0.03). There were no clinically significant changes during the study in plasma creatinine, plasma glucose, serum insulin, serum fasting lipids, or in any parameter associated with the calcium-parathyroid axis or the renal handling of calcium. There was no significant difference in the analysis of change in hoarseness between the two groups. There was a low incidence of oropharyngeal candidiasis during the study in both groups. Four patients (6%) in the fluticasone propionate group and one patient (2%) in the beclomethasone or budesonide group had evidence of candidiasis. There was no significant difference between the two groups. Thirty-four patients (51%) in the fluticasone propionate group and 36 patients (55%) in the beclomethasone/budesonide group reported one or more exacerbations during the course of the trial. There was a significant increase in the overall asthma quality of life score in the fluticasone propionate group (P<0.001); however, there was no significant difference in the beclomethasone or budesonide group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.13).
Raphael et al.[88] (1999) Fluticasone propionate 88 µg BID vs fluticasone propionate 220 µg BID vs beclomethasone 168 µg BID vs beclomethasone 336 µg BID	AC, DB, PG, RCT Nonsmoking patients 12 years of age or older with a diagnosis of chronic asthma requiring daily ICS therapy for at least six months prior to the study	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime awakenings and asthma symptoms	Primary: The FEV_1 was significantly improved from baseline in both treatment groups; however, greater improvements occurred with fluticasone propionate compared to beclomethasone (0.05 vs 0.03 L; P=0.006). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone propionate treatment groups improved by 0.31 (14%) and 0.36 L (15%) respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively. Secondary: The $FEF_{25\ to\ 75\%}$ and FVC were significantly improved from baseline in all treatment groups; however, patients receiving fluticasone propionate experienced greater improvements compared to patients receiving beclomethasone ($P \leq 0.034$ for all). Fluticasone propionate treatment provided a significantly greater improvement in morning PEF compared to beclomethasone treatment at all time points except week two ($P<0.004$ for all). There was a significant improvement in morning PEF relative to baseline in the fluticasone propionate group (15.8 to 22.8 L), but not in the beclomethasone groups (0.7 to 7.2 L; P values not reported). A similar trend was seen in evening PEF, but the differences between treatments was not statistically significant. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of albuterol-free days was significantly higher in the fluticasone propionate group compared to the beclomethasone group (P=0.01 at 14 weeks). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone propionate treatment groups, respectively, whereas it was unchanged in the beclomethasone low-dose group and decreased by 0.3 (9%) puffs/day in the moderate-dose group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences noted in the analysis of nighttime awakenings. Significant improvements in asthma symptom scores (P=0.024) and in the percentage of days in which no symptoms were recorded (P=0.027) occurred with fluticasone propionate treatment compared to beclomethasone treatment.
Ferguson et al.[89] (1999) Fluticasone propionate 200 µg BID via DPI vs budesonide 400 µg BID via DPI	AC, DB, DD, PG, RCT Children four to 12 years of age with a history of moderate to severe asthma who required moderate to high doses of an ICS to control symptoms for at least one month preceding the study	N=442 22 weeks	Primary: Mean morning PEF during the last seven treatment days Secondary: Adverse events	Primary: The adjusted mean morning PEF, measured over the last seven treatment days, were 271±82 and 259±75 L/minute, for the fluticasone propionate and budesonide treatment groups, respectively. The difference in means was 12 L/minute (90% CI, 6 to 19; P=0.002). For the purpose of this study, the two treatment regimens were considered to be equivalent if the 90% CI for the difference in mean morning PEFs for the last seven days of the 20-week treatment period were within ±15 L/minute. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/minute, respectively, indicating that the treatments were not equivalent, with fluticasone propionate demonstrating improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the two treatment groups.
Fitzgerald et al.[90] (1998) Fluticasone propionate 375 µg BID vs budesonide 750 µg BID	AC, DB, RCT, XO Children five to 16 years of age with persistent severe asthma requiring 1,000 to 2,000 µg/day of inhaled beclomethasone or budesonide continuously for symptom control over the previous 12	N=30 12 weeks	Primary: The daily mean morning and evening PEF and day and night symptom scores Secondary: Physician/patient/parent assessment of efficacy, total number of exacerbations	Primary: There was no statistically significant difference between the treatment groups in PEF or symptoms scores. Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone propionate and budesonide effective or very effective. The total number of exacerbations (33 in the fluticasone propionate group and 35 in the budesonide group) and those exacerbations requiring systemic steroids (nine in the fluticasone propionate group and 11 in the budesonide group) suggested no difference between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	months		requiring systemic steroids, adrenal function, growth and adverse events	There were no significant differences in adjusted means for urinary free cortisol levels, adrenocorticotropic hormone levels, or baseline and peak serum cortisol levels between the treatment phases. There was no significant treatment effect on growth which remained normal in either group. Most adverse events were related to exacerbations of asthma or upper respiratory tract infections. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to ICSs between the treatment groups.
Harnest et al.[91] (2008) Fluticasone propionate 500 µg BID vs mometasone 500 µg BID	AC, RCT Patients 18 years of age and older with moderate to severe persistent asthma who were previously using an ICS for daily maintenance therapy for ≥30 days	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue medication use, response to therapy and adverse events	Primary: The change from baseline in PEF was 7.8% in the mometasone group and 7.7% in the fluticasone propionate group (P=0.815). Secondary: At week 12, the change from baseline in FEV_1 was 0.4 L in both the mometasone and fluticasone propionate groups (P=0.988). The morning and evening asthma symptom scores were not significantly different between the mometasone and fluticasone propionate groups (P=0.251). Rescue albuterol use decreased from baseline in patients receiving either treatment; however, there was no significant difference between the groups (P=0.890). Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group and 43% of the patients in the fluticasone propionate group. The difference between the two groups was not significant (P value not reported).
Condemi et al.[92] (1997) Fluticasone propionate 250 µg	AC, DB, DD, PC, PG, RCT Patients 12 years of age and older with	N=291 24 weeks	Primary: Morning predose FEV_1, probability of remaining in the study over time,	Primary: Patients in both the fluticasone propionate and triamcinolone groups experienced statistically significant improvements in FEV_1 compared to the placebo group (0.27 and 0.07 vs -0.18 L for fluticasone propionate and triamcinolone compared to placebo, respectively; $P \leq 0.001$ for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs triamcinolone 200 µg QID vs placebo	asthma (FEV_1 50 to 80% of predicted value) who had previously received maintenance therapy with beclomethasone or triamcinolone		patient-measured PEF, albuterol use, number of nighttime awakenings requiring albuterol and asthma symptom scores Secondary: Adverse events and morning plasma cortisol levels	Only 27% of patients in the placebo group remained in the study over time compared to 66% of patients in the fluticasone propionate group and 55% of patients in the triamcinolone group. Patients in either active treatment group had a significantly greater probability of remaining in the study over time compared to patients in the placebo group (P<0.001). There was no significant difference between the two active treatment groups. The mean PEF was significantly improved in patients who received fluticasone propionate (21 L/minute) compared to mean decreases of six and 28 L/minute in the triamcinolone and placebo groups, respectively (P<0.001). Albuterol use was reduced by 30% in the fluticasone propionate group and by 6% in the triamcinolone group. Patients in the placebo group increased their albuterol use by 50% (P<0.05). The number of nighttime awakenings requiring albuterol was significantly decreased with either fluticasone propionate or triamcinolone compared to placebo (P≤0.001 for both). The frequency of nighttime awakenings significantly increased after treatment with placebo (P<0.05). There were no significant differences between the treatment groups with respect to symptom scores. Secondary: Thirteen percent of patients in the placebo group, 15% of patients in the fluticasone propionate group and 8% of patients in the triamcinolone group experienced at least one adverse event that was considered to be potentially treatment-related. One percent of patients in the placebo group, 3% of patient in the triamcinolone group and 1% of patients in the fluticasone propionate group had morning plasma cortisol concentrations <5 µg/mL.
Noonan et al.[93] (2009)	AC, MC, OL, PRO Patients four to 11	N=233 52 weeks	Primary: Incidence of adverse events	Primary: The incidence of adverse events was similar in all three groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mometasone 200 µg QD vs mometasone 100 µg BID vs beclomethasone 168 µg BID	years of age with mild to moderate persistent asthma using an ICS within 30 days prior to the study and on a stable regimen at least two weeks before screening		Secondary: Laboratory tests including cortisol concentrations, vital signs and physical examinations	Secondary: No significant differences between groups were observed in any secondary end points.
Nathan et al.[94] (2001) Mometasone 100 µg BID vs mometasone 200 µg BID vs beclomethasone 168 µg BID vs placebo	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously maintained on an ICS	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings and albuterol use	Primary: The FEV_1 was significantly improved in all three active treatment groups compared to the placebo group (P<0.01). There was no statistically significant difference in FEV_1 between the mometasone 200 µg and beclomethasone groups (P=0.07) or the mometasone 200 µg and mometasone 100 µg groups (P=0.08). Secondary: The improvements in FEV_1, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 µg group as for the mometasone 100 µg and beclomethasone groups; however, the difference was not significant.
Bernstein et al.[95] (1999) Mometasone 100 µg BID	AC, DB, DD, MC, RCT Patients with asthma previously treated with an ICS	N=365 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: FVC, $FEF_{25\ to\ 75\%}$,	Primary: The changes from baseline in FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and PEFR were significantly greater in all the active treatment groups compared to the placebo group (P<0.01 for all). The mometasone 200 µg BID group demonstrated a greater improvement compared to the mometasone 100 µg BID group, with the mometasone 400 µg BID group showing no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mometasone 200 µg BID vs mometasone 400 µg BID vs beclomethasone 168 µg BID vs placebo			PEFR, patient evaluation of asthma symptoms and physician evaluation of asthma symptoms	additional benefit. Secondary: Changes in lung function were similar between the mometasone 100 µg BID group and the beclomethasone group. Improvements in asthma symptoms as evaluated subjectively by patients and physicians were similar for the mometasone 200 (P<0.01) and 400 (P=0.05) µg BID groups, which were also significantly better than the mometasone 100 µg BID (P=0.01) and beclomethasone (P=0.02) treatment groups.
Bousquet et al.[96] (2000) Mometasone 100 to 400 µg BID vs budesonide 400 µg BID	AC, DB, MC, RCT Patients with moderate persistent asthma previously maintained on a daily ICS	N=730 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use and physician evaluation of response to therapy	Primary: The FEV_1 was significantly improved from baseline in the mometasone 200 and 400 µg BID treatment groups compared to the budesonide treatment group (P<0.05 for both). Secondary: Morning wheezing scores were significantly improved in the mometasone 400 µg BID group compared to the budesonide group and mometasone 100 µg BID group (P value not reported). Patients treated with mometasone 200 or 400 µg BID required significantly less albuterol compared to patients treated with budesonide. Physicians reported a significant improvement in asthma symptom scores in the mometasone 200 and 400 µg BID groups compared to the budesonide group (65 and 63 vs 50%; P value not reported).
Corren et al.[97] (2003)	AC, DB, DD, MC, PC, RCT	N=262 8 weeks	Primary: Percent change from baseline in	Primary: The percent change in FEV_1 was significantly greater in the mometasone group compared to the budesonide (P<0.01) and placebo groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mometasone 440 µg QD vs budesonide 400 µg QD vs placebo	Patients with moderate persistent asthma previously using ICSs		FEV_1 Secondary: Morning and evening PEFR, FVC, $FEF_{25\ to\ 75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy and asthma symptom scores	(P<0.001). Secondary: Pulmonary function ($FEF_{25\ to\ 75\%}$, FVC), evening asthma symptoms scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were significantly improved in the mometasone group compared to both the budesonide and placebo groups (P<0.05 for both).
Wardlaw et al.[98] (2004) Mometasone 400 µg QPM vs fluticasone propionate 250 µg BID	AC, OL, PG, RCT Patients with moderate, persistent asthma previously using fluticasone propionate	N=167 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: FVC, PEFR, asthma symptom scores, albuterol use and device evaluation	Primary: There were no significant differences in the percent change in FEV_1 between the groups at any point in the study (P≥0.14 for all). Secondary: There were no significant differences in the percent change in FVC (P≥0.24), PEFR (P=0.60), albuterol use or asthma symptom scores (P≥0.06) between the groups at any point in the study. A greater proportion of patients in the mometasone group experienced an improvement in asthma symptoms compared to the fluticasone propionate group (P=0.007) as reported by physicians' evaluations of response to therapy. A significantly greater proportion of patients reported having "liked the inhaler a lot" in the mometasone group compared to the fluticasone propionate group (P=0.01).
O'Connor et al.[99] (2001)	AC, DB, MC, PG, RCT	N=733 12 weeks	Primary: Change from baseline in FEV_1	Primary: Patients in either group experienced an improvement from baseline in FEV_1. There was no statistically significant difference between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mometasone 100 to 400 µg BID vs fluticasone propionate 250 µg BID	Patients with moderate, persistent asthma previously treated with an ICS		Secondary: Mean changes from baseline in PEFR, $FEF_{25\ to\ 75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to asthma and physician-evaluation of response to therapy	Patients in the mometasone 400 µg BID group experienced a significant improvement in FEV_1 compared to patients in the mometasone 100 µg BID group (P=0.02). Patients in the mometasone 200 µg BID and fluticasone propionate groups experienced similar improvements in FEV_1. Secondary: The $FEF_{25\ to\ 75\%}$ and PEFR were significantly improved in the mometasone 200 µg BID, 400 µg BID and fluticasone propionate groups compared to the mometasone 100 µg BID group. There were no statistically significant differences in the other outcomes between groups.
Lazarus et al.[100] (2019) Mometasone twice-daily (at a dose of 220 µg with the Asmanex Twisthaler or 200 µg with the Asmanex HFA) vs tiotropium once-daily (at a dose of 5 µg with Spiriva Respimat vs placebo twice-daily	DB, MC, XO Patients ≥12 years of age who had mild, persistent asthma. Patients were categorized according to the sputum eosinophil level (<2% or ≥2%)	N=295 42 weeks	Primary: Response (determined according to a hierarchical composite outcome that incorporated treatment failure, asthma control days, and the FEV_1) among patients with a low sputum eosinophil level who had a prespecified differential response to one of the trial agents; a two-sided P-value <0.025 denoted statistical significance	Primary: A total of 73% of the patients had a low eosinophil level; of these patients, 59% had a differential response to a trial agent. However, there was no significant difference in the response to mometasone or tiotropium, as compared with placebo. Among the patients with a low eosinophil level who had a differential treatment response, 57% (95% CI, 48 to 66) had a better response to mometasone, and 43% (95% CI, 34 to 52) had a better response to placebo (P=0.14). In contrast 60% (95% CI, 51 to 68) had a better response to tiotropium, whereas 40% (95% CI, 32 to 49) had a better response to placebo (P=0.029). Secondary: Among patients with a high eosinophil level, the response to mometasone was greater than the response to placebo (74% vs 26%) but the response to tiotropium was not (57% vs 43%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: A comparison of results in patients with a high sputum eosinophil level and those with a low level	
Kramer et al.[101] (2013) Ciclesonide vs budesonide vs fluticasone propionate	MA (6 RCTs) Patients <18 years of age with chronic asthma	N=3,256 ≥4 weeks	Primary: Asthma symptoms, asthma exacerbations, adverse effects Secondary: Quality of life, compliance, change in lung function and airway inflammation	Primary: There were two studies included that evaluated ciclesonide for non-inferiority to budesonide. There were no significant differences in asthma symptoms or exacerbations. Rates of adverse effects were similar between the two treatments. Four studies compared ciclesonide to fluticasone propionate. There were no significant differences in asthma symptoms, asthma exacerbations and adverse effects. However, in the one study that compared ciclesonide and fluticasone propionate in a 1:2 dose ratio, the number of asthma exacerbations was significantly higher in the ciclesonide group (RR, 3.57; 95% CI, 1.35 to 9.47). Secondary: When ciclesonide was compared to budesonide, there were no significant differences in quality of life measures and FEV_1. No other secondary endpoints were reported. For the studies comparing ciclesonide and fluticasone propionate, non-inferiority of ciclesonide was confirmed for quality of life measures (P<0.0001). There were no significant differences in FEV_1. No other secondary endpoints were reported.
Szefler et al.[102] (2007) Budesonide 500 µg QD (BIS group) vs	MC, OL, RCT Children 2 to 8 years of age with symptoms of mild persistent asthma	N=695 52 weeks	Primary: Time to first additional medication for asthma worsening over 52 weeks	Primary: Time to first additional asthma medication over a period of 52 weeks was not significantly different (P=0.285) between the two groups. Secondary: Percentages of subjects who received ≥1 course of additional asthma medication over the 52-week treatment period in BIS group vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
montelukast 4 to 5 mg QD			Secondary: Time to first additional asthma medication measured at 12 and 26 weeks; time to first asthma exacerbation measured at 12, 26, and 52 weeks; exacerbation rates over a period of 52 weeks; diary variables: daily AM and PM PEF, and symptom scores; patient/caregiver-reported outcomes via standardized questionnaires	montelukast group were as follows: 12 weeks (29.1 vs 38.6%, respectively), 26 weeks (41.3 vs 48.2%, respectively), and 52 weeks (52.0 vs 56.9%, respectively). Subjects treated with BIS experienced a lower rate of exacerbations (number/subject/year) that required step-up BIS therapy or oral corticosteroids vs subjects treated with montelukast (1.23 vs 1.63, respectively; unadjusted P=0.034; a 24.5% reduction in the total number of exacerbations). Percentages of subjects who received oral corticosteroids for an acute severe exacerbation over the 52-week treatment period in BIS group vs montelukast group were as follows: week 12 (10.7 vs 14.7%, respectively), week 26 (17.3 vs 22.3%, respectively), and week 52 (25.5 vs 32.0%, respectively). Rate (number/subject/year) of acute severe exacerbations requiring treatment with oral corticosteroids was lower in BIS group vs montelukast group (0.52 vs 0.67, respectively; P=0.149), with an estimated reduction in the total number of courses of additional oral corticosteroid therapy of 22.7% in BIS group vs montelukast group. *Diary variables: short-term results* Mean changes from baseline to the average over the first 12 weeks in secondary diary variables generally were similar in both treatment groups, with the exception of AM and PM PEF, for which improvements were greater in BIS group vs montelukast group (morning PEF, unadjusted P=0.007; evening PEF, unadjusted P=0.005). Mean daytime and nighttime asthma symptom scores showed greater improvements in BIS group vs montelukast group, although the differences were not significant (adjusted mean change from baseline, –0.40 vs –0.35 and –0.43 vs –0.35, respectively). Mean changes from baseline to the average over the first 12 weeks in the daily use of rescue medication were similar in both treatment groups). *Diary variables: long-term results* Improvements from baseline in all diary variables were greater over a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				period of 52 weeks compared with 12 weeks in both treatment groups. Similar results were observed in BIS and montelukast groups on all variables over a period of 52 weeks, with the exception of AM and PM PEF, for which the mean changes from baseline were greater with BIS compared with montelukast (AM PEF, 28.39 vs 20.63, respectively; PM PEF, 25.25 vs 16.85, respectively). Improvements from baseline to the average over the first 12 weeks in spirometry variables (FEV_1, FVC and % predicted FEV_1) were small in both treatment groups, with no significant differences observed between the groups. Patient-reported outcomes and global assessments were evaluated by using the Child Health Questionnaire Parent Form-50 (CHQ-PF50), the Children's Health Survey for Asthma (CSHA), the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ), and the Global Physician and Caregiver Assessments. Results of Physician and Caregiver Global Assessments were significantly better ($P \leq 0.0164$) for BIS compared with montelukast at week 12. The results of Physician Global Assessments also were significantly better ($P \leq 0.0171$) for BIS compared with montelukast at the end of treatment. The results of the CHQ-PF50 questionnaire, the CHSA, and the PACQLQ generally were similar between the groups at the end of week 12.
Nakanishi et al.[103] (2003) Flunisolide 1 mg BID via valved holding chamber vs prednisone 2 mg/kg	PC, PG, RCT, Masked Children 6 to 16 years of age seeking emergent care for an acute exacerbation of asthma	N=58 7 days	Primary: Percentage of predicted FEV_1 Secondary: Symptom score, initial vital signs and oximetry, side effects, recurrence rate for acute asthma symptoms, and daily PEF Secondary: Not reported	Primary: The FEV_1 percentage of predicted for the ICS group was lower on day three (65 vs 78% for oral corticosteroids; P=0.03) and on day seven (77 vs 95%; P=0.002). Both groups continued to improve over the seven-day study period, with the most improvement in those patients receiving oral corticosteroids. Secondary: There was no significant difference in symptom severity between the two groups at any time during the study. There was no significant difference in initial vital signs or oximetry between the two groups at any time during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				One patient in the ICS group required additional corticosteroids after the seven-day study period to control symptoms. One patient in the oral corticosteroid group required hospital admission for asthma within 24 hours following enrollment. There was no significant difference in PEF between the two groups at any time during the study.
Pohl et al.[104] (2006) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide 320 µg, 2 inhalations BID (AMD)	DB, PG, RCT Patients >19 years of age with asthma, FEV_1 reversibility ≥15% (or 200 mL) within 1 month prior to enrollment, FEV_1 40 to 85% of predicted normal, requirement with an ICS or ICS/LABA combination within given starting dose range	N=133 20 weeks	Primary: Number of patients/ treatment group with ≥1 treatment failure (defined as hospitalization, oral steroids, nebulized β_2-agonists, withdrawal due to lack of efficacy or life-threatening condition) Secondary: HRQOL measured by the SF-36, dose of study medication, days of reliever medication use, and treatment satisfaction	Primary: The rate of treatment failures were comparable between the two treatment groups with five out of the 63 patients in the budesonide/formoterol group and two out of the 63 patients in the budesonide group experiencing treatment failure throughout the duration of the study. Secondary: Patients in the budesonide/formoterol group had a statistically significant improvement in HRQOL and treatment satisfaction (for patients and physicians) vs those in the budesonide group (P<0.05). Patients in the budesonide/formoterol group also had a lower use of daily inhalations of study drug vs budesonide (P=0.024). Both groups had minimal use of reliever medications.
Tal et al.[105] (2002) Budesonide-formoterol 80-4.5 µg, 2 inhalations	DB, DD, MC, PG, RCT Children 4 to 17 years of age with a diagnosis of asthma	N=286 12 weeks	Primary: Morning PEF Secondary: FEV_1, FEV_1 over a 12 hour time	Primary: Combination therapy resulted in a significantly greater increase in morning PEF than monotherapy (P<0.001). Results were similar for evening PEF (P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs budesonide 100 µg, 2 inhalations BID	for ≥6 months, FEV_1 40 to 90% of predicted value at visit 1, >15% reversibility of FEV_1 within 15 minutes of inhalation of a SABA, 6 weeks constant dosing with an ICS (budesonide, fluticasone propionate or beclomethasone)		period, rescue inhaler use, comparison of nocturnal asthma symptoms, and safety	FEV_1 scoring (P<0.05), mean improvement of FEV_1 over 12 hours after one dose (P<0.05) and mean improvement of FEV_1 ten minutes after first dose (P<0.05) favored combination therapy. A decrease in rescue inhaler use from 0.71 to 0.60 inhalations/day was seen in the combination therapy group, and a change of 0.50 to 0.41 inhalations was seen with the monotherapy group. There was no statistical significance between the groups (P value not reported). A decrease in the number of nights awakening with asthma symptoms was seen in both groups with no significant difference (combination therapy decreased from 7.2 to 5.5% and monotherapy decreased from 8.5 to 6.6%; P value not reported). Reported adverse events between the two groups were comparable and reported as combination vs monotherapy. Pharyngitis (8 vs 12%), respiratory infection (8 vs 6%), rhinitis (7 vs 4%), coughing (5 vs 5%), headache (6 vs 4%), viral infection (7 vs 3%), fever (6 vs 2%) and aggravated asthma (5 vs 3%). In the combination therapy group, 4.7% of patients had serious adverse side effects.
Lalloo et al.[106] (2003) Budesonide-formoterol 80-4.5 µg BID vs budesonide 200 µg BID Inhaled terbutaline or salbutamol was used as a reliever medication depending on	DB, MC, PG, RCT Patients >18 years of age with a diagnosis of asthma assessed by the following: FEV_1 60 to 90% of predicted normal value and >12% reversibility of basal FEV_1 within 15 minutes of terbutaline or salbutamol inhalation; all patients received	N=467 12 weeks	Primary: Morning and evening PEF values Secondary: FEV_1/FVC measurements, symptom free days, reliever free days, nighttime awakenings, time to first mild and severe exacerbation, and safety	Primary: Morning and evening PEF values increased for both treatment groups; however, significantly larger increases were seen with combination therapy than with monotherapy (P=0.002 and P<0.001, respectively). Secondary: Mean FEV_1 scores increased in both groups but no significant difference was found, additionally, FVC showed no change from baseline. The incidence of asthma control days, symptom free days and reliever medication use (P=0.025) all favored combination therapy. Asthma control days favored combination therapy (17 vs 10%; P=0.002). Symptom free days were similar between groups (16 vs 10%; P=0.007). A reduction of 24 vs 6% and 23 vs 14% favored combination therapy for asthma symptom score and nighttime awakenings, respectively (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
patient preference.	ICSs of any brand at a constant dose of 200 to 500 µg/day for ≥1 month prior to study entry			Fewer patients experienced a mild exacerbation (110/230) in the combination group than the monotherapy group (136/237; P value not reported). Nighttime awakenings also favored combination therapy (75 vs 105; P value not reported). The monotherapy group showed a shorter time to first mild exacerbation compared to the combination group (P=0.02). The risk of having a mild exacerbation was estimated to be 26% lower in the combination group (P=0.02). The chance of having a severe exacerbation was six percent lower in the combination group (P=0.85). No between group differences were noted for the profile and frequency of adverse events. Both treatment groups commonly reported respiratory infection, pharyngitis, and rhinitis. Overall, there were seven severe adverse events, five occurred with combination therapy and two with monotherapy.
Berger et al.[107] (2010) Budesonide-formoterol 160-4.5 µg BID vs budesonide 200 µg BID	MC, OL, RCT Patients 6 to 11years of age with asthma for ≥ 6 months who previously received daily ICS for ≥4 weeks prior to randomization and had FEV_1 ≥50%	N=187 26 weeks	Primary: Safety analysis, urinary cortisol, EKG's Secondary: Pulmonary function, health care resource utilization, HRQL	Primary: The incidence of adverse reactions was similar between both groups, with 84.6% of events occurring in the budesonide-formoterol group and 85.7% of events occurring in the budesonide group. No serious adverse events were considered related to the treatment drug. No hyperglycemia, hypokalemia or differences in urinary cortisol were detected and no other significant differences were noted on physical exam. Secondary: There was a mean improvement of FEV_1 from baseline favoring budesonide-formoterol vs budesonide (0.15 vs 0.07 L; P<0.01). There were significant improvements from baseline to end of therapy in both groups, and a greater improvement in the budesonide-formoterol group compared to budesonide, in the Pediatric asthma caregiver quality of life questionnaire (PACQLQ). These differences did not meet the prespecified minimally important differences.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients in the budesonide-formoterol group had significantly fewer visits to urgent care facilities compared to budesonide group (3.3 vs 11.1%, respectively; P<0.05).
Zangrilli et al.[108] (2011) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg, 2 inhalations BID via MDI	AC, DB, MC, RCT Hispanic patients ≥12 years of age with asthma for ≥6 months and a pre-bronchodilator FEV_1 of 45 to 85% of predicted normal and reversibility of ≥12% with albuterol administration and a documented daytime or nighttime asthma symptom scores ≥0 on 3 or more days within 7 consecutive days during a 2-week run-in period on budesonide 160 µg BID	N=150 12 weeks	Primary: Mean change from baseline in morning (AM) PEF Secondary: Predefined asthma events (decreased FEV_1 ≥20% from randomization or FEV_1 <40% of predicted normal, ≥12 inhalations of albuterol per day, decreased morning PEF ≥20% from baseline on ≥3 of seven consecutive days after randomization, ≥2 nocturnal asthma awakenings requiring rescue medication within seven days after randomization, or a clinical exacerbation requiring emergency	Primary: The morning PEF value increased from baseline during randomized treatment, in both treatment groups but there was no significant difference between treatments (25.4 vs 19.9% in the combination and monotherapy groups, respectively; P≥0.428). Secondary: Patients who received combination therapy experienced fewer asthma events compared to patients receiving monotherapy, although the difference was not statistically significant (25.2 vs 31.7%; P value not reported). Similarly, 3.1 and 6.5% of patients in the combination and monotherapy treatment groups withdrew from the study due to asthma related events, although the differences in discontinuation rates were not significant (P value not reported). There was no significant difference between patients receiving combination treatment or monotherapy, in regard to the change in daily asthma symptom score, daytime symptom score or nighttime symptom score (P≥0.181 for all comparisons). Rescue medication use decreased, and the percentage of symptom-free days, awakening-free nights, and rescue medication-free days increased in both treatment groups, but no differences in these outcomes were observed between the treatment groups (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment, hospitalization, or use of an excluded asthma medication) and withdrawals caused by these events, pulmonary function assessments and diary-based measures of asthma control	
Spector et al.[109] (2012) Budesonide-formoterol 320-9 µg BID vs budesonide 320 µg Each group had a two week run-in period with single-blinded budesonide 180 µg BID.	DB, DD, RCT Self-reported black patients ≥12 years of age with an asthma diagnosis for ≥6 months, FEV_1 of 45 to 85% predicted normal, reversibility of FEV_1 ≥12% and ≥0.2 L, and consistent treatment with daily medium- to high-dose ICSs for ≥30 days	N=311 12 weeks	Primary: Change from baseline in predose FEV_1 at weeks two, six, 12 Secondary: Change from baseline in FVC, FVC in middle portion of expiration, diary-related assessments (morning and evening PEF, asthma symptoms, rescue medication use, nighttime awakenings, awakening fee nights, rescue medication free days, asthma control days) and	Primary: Improvements in predose FEV_1 was significantly greater in the budesonide-formoterol group compared to the budesonide group (P=0.008) at 12 weeks. Significant differences in predose FEV_1 started at week two and continued throughout the time points (P≤0.032). Secondary: The improvement in predose FVC was significantly greater in the budesonide-formoterol group compared to the budesonide group (P<0.05). However the improvement in FVC in middle portion of expiration was not significantly different between the groups. Improvements in morning and evening PEF was significantly greater in the budesonide-formoterol group compared to the budesonide group (P<0.001). The rate of asthma worsening was lower in the budesonide-formoterol group compared to the budesonide; however, the difference was not statistically significant. Compared to the budesonide group, reductions in daily asthma symptoms (P=0.039) and rescue medication use (P=0.029) were significantly greater in the budesonide-formoterol group. Improvements in awakening fee nights, rescue medication free days, and asthma control days were not significantly different between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			asthma worsening	In the budesonide-formoterol group, 41.2% of patients experienced and adverse event compared to 30.3% in the budesonide group. The most comment adverse events in both groups were headache, nasopharyngitis and upper respiratory infection.
Brown et al.[110] (2012) Budesonide-formoterol 320-9 µg BID vs budesonide 320 µg BID Each group had a two week run-in period with single-blinded budesonide 180 µg BID.	DB, MC, PG, RCT Self-reported African American patients ≥12 years of age with stable asthma for ≥6 months, FEV_1 ≥50% predicted normal value at screening and randomization, reversibility of FEV_1 ≥12% and ≥0.2 L, and consistent treatment with daily medium-to high-dose ICSs for ≥30 days	N=752 52 weeks	Primary: Change in asthma exacerbations and adverse events Secondary: Changes in FEV_1, FVC, patient daily diary measure of asthma control (rescue medication usage, rescue medication free days, symptoms free days and asthma control days)	Primary: There percentage of patients with ≥1 asthma exacerbation was significantly lower in the budesonide-formoterol group compared to the budesonide group (P=0.006). The rate of asthma exacerbations was significantly reduced in the budesonide-formoterol group compared budesonide (P=0.002). The rate of prednisone usage was significantly reduced in the budesonide-formoterol group compared budesonide (P<0.001). In the budesonide-formoterol group, 51.2% experienced ≥1 adverse events compare to 47.8% in the budesonide group. Adverse events that were reported in ≥5% of patients included headache (8.6%), nasopharyngitis (7.4%), sinusitis (5.1%) and viral upper respiratory tract infection (5.1%). In the budesonide-formoterol group and budesonide, there were similar rates of discontinuation due to adverse events (2.7 and 2.2%), serious adverse events (3.2 and 4.1%) and nonfatal serious adverse events (2.9 and 3.8%). Secondary: Improvements in FEV_1, FVC and morning PEF were significantly greater with budesonide-formoterol group compared budesonide (P≤0.013). Additionally, there was significant improvements with budesonide-formoterol group compared budesonide in percentage of rescue medication-free days (P=0.003) and asthma control (0.006). There was no significant difference in symptom-days. Reductions in rescue albuterol metered dose inhaler usage was significantly higher in the budesonide-formoterol group compared budesonide (P=0.0030).
Remington et al.[111] (2002) Budesonide (range: 200, 400, and 800 µg)	MA Patients ≥12 years of age with mild to severe asthma	N=4,079 (5 trials) 12 weeks to 12 months	Primary: Frequency of mild and severe exacerbations, time to first severe exacerbation,	Primary: The addition of formoterol to high-dose budesonide resulted in a greater reduction in both mild and severe exacerbation rates compared to low-dose budesonide (P<0.001). High-dose budesonide monotherapy was more efficacious in reducing the rates of severe exacerbations in comparison to low-dose budesonide and formoterol (P=0.03), but similar

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide (range: 200, 400, and 800 µg) plus formoterol (range: 9 to 24 µg)			poorly controlled asthma days, PEF, asthma symptoms, rescue medication use Secondary: Not reported	results were observed between the two groups in regards to the rate of mild exacerbations. The addition of formoterol to either budesonide 200 or 400 µg in patients who were previously on low-medium doses of ICS led to a greater reduction in the risk of first severe exacerbation, as well as a reduction in the frequency of poorly controlled asthma days compared to budesonide alone. Combination of budesonide and formoterol in separate devices or a single inhaler had significantly greater improvements in morning PEF compared to budesonide alone (P<0.0001), and improvements were maintained over the entire study period. Combination therapy was associated with grater improvements in symptom scores, symptom-free days, and rescue medication use. There were no observed differences between the treatment groups in regard to the number of severe exacerbations. Budesonide and formoterol were equally efficacious, whether in a single or separate inhaler, and were more effective than budesonide alone. Patients in the high dose budesonide plus formoterol group had improved AQLQ scores during both the run-in period and during the treatment period (P<0.001 and P=0.028, respectively). Secondary: Not reported
Rosenhall et al.[112] (2002) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler)	MC, OL, RCT Patients with moderate persistent asthma (average age, 45)	N=586 6 months	Primary: Safety and efficacy (FEV_1, Mini AQLQ, ACQ, exacerbations Secondary: Not reported	Primary: Patients in both treatment groups had a mean FEV_1 increase of five to six percent from baseline (P value not reported). There was no significant change in response using the Mini AQLQ and the ACQ from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency (P value not reported). The withdrawal rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers)				in both groups was also similar (P=0.085). Secondary: Not reported
Rosenhall et al.[113] (2003) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers)	MC, OL, PG, RCT Adult patients with asthma of ≥6 months duration, predicted FEV_1 ≥50%, receiving constant ICS dose of ≥400 to 1,200 µg for ≥30 days, and daily use of inhaled short- and/or LABA	N=321 6 months	Primary: Lung function, asthma control, HRQOL Secondary: Adverse events	Primary: There were no significant differences in lung function measurements, time to first exacerbation (defined as first use of oral glucocorticosteroids), or HRQOL observed between treatment groups. Secondary: There were no significant differences in incidence and severity of adverse events observed between treatment groups. More patients from the budesonide-formoterol group than the budesonide plus formoterol group remained in the study (P=0.008).
Rosenhall et al.[114] (2006) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations	ES, MC, OL, PG, RCT Adult patients with asthma	N=320 12 months	Primary: Efficacy and safety parameters Secondary: Not reported	Primary: There were no significant differences observed between the two treatment groups in regards to safety and efficacy. There was a lower withdrawal rate in patients treated with budesonide-formoterol via a single inhaler compared to those using separate inhalers (9.2 and 19.4%, respectively; P=0.008). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID (separate inhalers)				
Peters et al.[115] (2016) Budesonide and formoterol 80/4.5 µg or 160/4.5 µg two puffs inhaled BID vs budesonide 80 µg or 160 µg two puffs inhaled BID (patients were stratified to a dose of budesonide based on pre-study asthma control as assessed by ACQ-6 and prior asthma therapy)	DB, MC, RCT Patients ≥ 12 years of age with a diagnosis of persistent asthma, daily asthma medication use, and with one to four asthma exacerbations in the previous year.	N= 11,693 26 weeks	Primary: First serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization) Secondary: First asthma exacerbation, asthma control, and symptom control	Primary: A serious asthma-related event occurred in 43 patients who were receiving budesonide-formoterol and in 40 patients who were receiving budesonide alone (HR, 1.07; 95% CI, 0.70 to 1.65). Budesonide-formoterol was shown to be noninferior to budesonide alone. There were two asthma-related deaths, both in the budesonide-formoterol group. One of these patients had undergone an asthma-related intubation. Secondary: In the budesonide-formoterol group, 539 patients (9.2%) reported a total of 637 exacerbations. In the budesonide group, 633 patients (10.8%) reported a total of 762 exacerbations. The risk of an asthma exacerbation was 16.5% lower with budesonide-formoterol than with budesonide alone (HR, 0.84; 95% CI, 0.74 to 0.94; P=0.002). There was a statically significant improvement in asthma control in both treatment groups. A greater improvement was observed with budesonide-formoterol (average decrease from baseline ACQ-6, −0.67) than with budesonide alone (average decrease from baseline ACQ-6, −0.58) P<0.001. Budesonide-formoterol was superior to budesonide alone in all of the variables assessed related to symptom control (including a greater mean number of symptom-free days, fewer night-time awakenings, and the use of fewer doses of rescue medication), except for limitation of activity because of asthma.
Rabe et al.[116] (2006) Budesonide-formoterol 160-4.5 µg BID and terbutaline MDI 0.4 mg as	DB, MC, PG, RCT Patients >12 years of age with asthma who had >1 severe asthma exacerbation in the 12 months before entry, use of	N=3,394 12 months	Primary: Time to first severe exacerbation Secondary: Total number of severe exacerbations, time	Primary: The time to first severe exacerbation was longer with as needed budesonide-formoterol vs formoterol (P=0.0048) or terbutaline (P<0.0001). As-needed formoterol prolonged the time to first severe exacerbation vs terbutaline (P=0.0051). Secondary: As-needed budesonide-formoterol reduced the risk of a severe

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
needed vs budesonide-formoterol 160-4.5 µg BID and formoterol MDI 4.5 µg as needed vs budesonide-formoterol 160-4.5 µg BID and budesonide-formoterol 160-4.5 µg as needed	inhaled corticosteroids for >3 months and at a constant dose for ≥4 weeks immediately before entry, FEV_1 50 to 100% of predicted normal (pre bronchodilator) with 12% reversibility or more after inhalation of terbutaline 1 mg		to first and total number of emergency treatment or hospitalizations, asthma symptom scores—asthma control questionnaire score; mild exacerbations; FEV_1; morning and evening PEF; and reliever medication use	exacerbation by 27% (95% CI, 10 to –41) vs formoterol and by 45% (95% CI, 32 to 55) vs terbutaline. The risk reduction with as-needed formoterol vs terbutaline was 24% (95% CI, 8 to 37). The yearly rate of severe exacerbations per patient was reduced with as-needed budesonide-formoterol by 33% vs formoterol (P<0.0001), by 48% vs terbutaline (P<0.0001), and by 22% with as-needed formoterol vs terbutaline (P=0.012). Rates of exacerbations needing emergency room treatment or hospitalization were reduced with as-needed budesonide-formoterol by 27% (P=0.046) vs formoterol and by 39% (P=0.0010) vs terbutaline, respectively. There was no significant difference between formoterol and terbutaline. The proportion of patients with more than one exacerbation was lowest in the as-needed budesonide-formoterol group (3, 7, and 7% of patients in the as-needed budesonide-formoterol, formoterol, and terbutaline groups, respectively). Mild exacerbation days were reduced by 10 to 18% with as-needed budesonide-formoterol compared with both formoterol P=0.043) and terbutaline (P<0.0001). The time to first mild exacerbation was longer with as-needed budesonide-formoterol vs terbutaline (P=0.0080), but the difference between as-needed budesonide-formoterol and formoterol was not significant (P=0.059). Mean asthma symptom scores decreased for all groups, with a greater reduction in the budesonide-formoterol for maintenance and reliever therapy group vs maintenance therapy plus formoterol (P=0.0002) or terbutaline (P=0.0007). Night-time awakenings were reduced by 2% (seven nights per year) with as-needed budesonide-formoterol vs formoterol (P=0.018) and by 3% vs terbutaline (P=0.0025). No between-group differences were seen with as-needed formoterol compared with terbutaline for asthma symptom scores or night-time awakenings.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Asthma-control days increased in all groups with no between-group differences. Overall ACQ-5 scores improved to a greater extent with as-needed budesonide-formoterol than with formoterol (P=0.0009) and terbutaline (P<0.0001). No difference in overall ACQ-5 scores was seen with formoterol vs terbutaline. Mean FEV_1 improved in each of the treatment groups when all patients used maintenance budesonide-formoterol plus as-needed terbutaline (run-in). Additional increases in FEV_1 of 0.05 and 0.08 L were seen with as-needed budesonide-formoterol vs formoterol (P=0.0001) and terbutaline (P<0.0001). Mean morning PEF increased from run-in in all groups, with a small additional improvement observed with as-needed budesonide-formoterol vs both formoterol (4.8 L per min; P=0.004) and terbutaline (7.5 L per min; P<0.0001). Similar improvements were noted with as-needed budesonide-formoterol for mean evening PEF compared with formoterol (5.4 L per min; P=0.0011) and terbutaline (6.3 L per min; P=0.0001). There was no significant difference in morning or evening PEF between as-needed formoterol and terbutaline. The mean reliever use decreased to 1.02 inhalations per day in the budesonide-formoterol group and to 1.23 and 1.26 inhalations per day in the formoterol and terbutaline groups, respectively. Patients receiving budesonide-formoterol used fewer as-needed inhalations per day than those receiving formoterol or terbutaline (P<0.0001 for both) and on 52% of treatment days patients in the budesonide-formoterol group did not use any as-needed medication compared with 48% in both comparator groups. There was no significant difference in reliever use between the formoterol and terbutaline groups.
Canonica et al.[117] (2004) CAST	RCT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations and	Primary: Both FD and AMD budesonide/formoterol treatment groups had similar low frequency of exacerbations, as well as improved comparable lung function. However, results did not reach statistical significance (P value

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol 80-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 80-4.5 µg, 2 inhalations BID (FD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (FD)			changes in asthma symptom severity Secondary: Asthma control, safety and health economics	not reported). Secondary: Both treatment groups had improved lung function, less asthma symptoms and fewer nighttime awakenings compared to the mean value of the run-in period (P value not reported). Patients in the AMD budesonide/formoterol dose group utilized 24% less of the study drug in comparison to those in the FD group (2.95 vs 3.86 daily inhalations, respectively; P<0.0001).
Berger et al.[118] (2010) Budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI vs budesonide-formoterol 160-4.5	AC, DB, DD, MC, PC, RCT Patients ≥16 years of age with a documented diagnosis of asthma for ≥6 months, mild to moderate persistent asthma based on ICS use and pulmonary	N=752 12 weeks	Primary: Pulmonary function (evening PEF as primary outcome) Secondary: Daytime and nighttime symptom scores, nighttime awakenings, rescue medication use,	Primary: For pulmonary function variables (evening PEF and evening pre-dose FEV_1) at the end of QD administration, all combination therapy groups were significantly (P<0.001) more effective than placebo. Compared to budesonide, results for evening PEF significantly favored combination therapy (P<0.001), whereas results for evening pre-dose FEV_1 significantly favored budesonide/formoterol BID (P<0.001). For both evening PEF and evening pre-dose FEV_1, significant differences were observed between the budesonide/formoterol BID and QD groups, favoring BID administration (P≤0.010). There were no significant differences in pulmonary function variables between the two combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg, 2 inhalations QD via MDI vs budesonide-formoterol 80-4.5 µg, 2 inhalations QD via MDI vs budesonide 160 µg, 2 inhalations QD via MDI vs placebo All patients discontinued their current asthma therapy and received SB treatment with budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI and rescue albuterol as needed during a 4 to 5-week run-in period.	function, previous use of low to medium dose ICS during the month prior to enrollment and a pre bronchodilator FEV_1 60 to 90%, with bronchodilator reversibility to albuterol of ≥12% and ≥0.20 L in FEV_1		events of and patient withdrawals from the trial because of predefined criteria for worsening asthma control, and AQLQ	therapy QD groups. Secondary: Changes from baseline in all rescue medication use and symptom-related variables were significantly better for all combination therapy groups vs placebo (P<0.001 for all). Compared to budesonide, significantly (P≤0.045) better results were observed for all rescue medication use and symptom-related variables with the combination therapy BID and QD (320-9 µg/day) groups. Over the 12 week period, the percentage of patients with a symptom-free day was greater in all combination therapy groups compared to budesonide and placebo. Nighttime asthma control variables were similar in the budesonide-formoterol QD and BID groups; however, BID administration showed significantly better results than QD (160-9 µg/day) administration for all other asthma control variables (P≤0.020). For combination therapy, significant differences in favor of BID administration compared to QD administration (320-9 µg/day) were observed for asthma control days (P=0.030) and daytime rescue medication use (P=0.050). Significant differences in favor of the higher QD dose (320-9 µg/day) compared to the lower (160-9 µg/day) QD dose were observed for symptom-free days, asthma control days and rescue medication-free days (P≤0.040). The percentage of patient with events of or withdrawals due to worsening asthma control were significantly lower for all combination therapy groups compared to placebo (P<0.001 for all), and for budesonide-formoterol BID and QD (160-9 µg/day) compared to budesonide (P≤0.028). In addition, significantly fewer patients in the budesonide-formoterol BID, budesonide-formoterol QD (320-9 µg/day) and budesonide groups met the criterion of clinical asthma exacerbation compared to placebo (P<0.01). Results were not significantly different between the combination therapy groups for these variables. Mean changes from baseline in AQLQ overall and all domain scores were significantly more favorable (P≤0.010), and differences were clinically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				meaningful, for all combination therapy groups compared to placebo, with the exception of the environmental exposure domain, for which clinically meaningful differences between placebo were observed only for budesonide-formoterol BID.
Jenkins et al.[119] (2006) Budesonide-formoterol 320-9 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 400 µg plus formoterol 9 µg, 2 inhalations BID (separate inhalers) vs budesonide 400 µg, 2 inhalations BID for 12 weeks, followed by either budesonide-formoterol or budesonide plus formoterol via separate inhalers for 12 weeks Terbutaline 0.5 mg was used throughout the	DB, DD, MC, RCT Outpatients >12 years of age with a diagnosis of asthma for ≥6 months, FEV_1 40 to 85% of predicted, >15% reversibility in increase from baseline FEV_1 after inhalation of a bronchodilator (for patients >18 years of age an increase of >200 mL, 15 to 30 minutes post bronchodilator); all patients used ICSs for >4 months before study entry at a daily dose >750 µg for >4 weeks, patients required an asthma symptoms score of >1 for ≥4 of 7 days of the run-in period	N=456 24 weeks	Primary: Morning and evening PEF Secondary: Adherence to therapy, FEV_1, symptom free days and nights, total number of reliever inhalations recorded in diary, daytime/nighttime symptom scores via diary, and safety	Primary: Patients receiving combination therapy had greater increases from baseline PEF scoring in both the morning and evening with 37.4 and 4.5 L/minute respectively (P<0.001). There was no significant difference between either of the combination therapies (P value not reported). Secondary: FEV_1 increased over time for all three treatment groups. However, those receiving combination therapy compared to monotherapy showed significant improvement (0.30 vs 0.14 L, respectively; P<0.001). Combination therapy reduced asthma symptom scores significantly better than monotherapy alone (P=0.0051). Patients receiving combination therapy had 16% more symptom free days than budesonide alone (P<0.001), used 0.97 inhalations of reliever medication/day compared to 1.61 for budesonide alone (P<0.001), had 19% more reliever free days (P<0.001) compared to budesonide alone, and resulted in 16% more asthma-control days, which is approximately 58 more days a year with asthma control (P<0.001) compared to budesonide alone. Combination therapy reduced the risk for mild exacerbation by 36% (P=0.0032). Combining budesonide/formoterol in one inhaler reduced the risk of mild exacerbation by 17% compared to separate inhaler therapy (P=0.13).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
study for as-needed relief.				
Kuna et al.[120] (2006) Budesonide-formoterol 80-4.5 µg, 2 inhalations in the evening vs budesonide-formoterol 80-4.5 µg, 1 inhalation BID vs budesonide 200 µg, 1 inhalation in the evening	AC, DB, DD, PG, RCT Adult patients with mild to moderate persistent asthma who were not optimally controlled on an ICS dose of 200 to 500 µg/day, mean predicted FEV_1 at baseline was 78.5%	N=617 12 weeks	Primary: Morning PEF Secondary: Evening PEF, symptom-free days, reliever-free days, asthma control days, and adverse events	Primary: Patients in both budesonide/formoterol regimens showed greater improvements in morning PEF (P<0.05). Secondary: Patients in both budesonide/formoterol regimens showed greater improvement in evening PEF, symptom-free days, reliever-free days and asthma-control days compared to the budesonide regimen (P<0.05). Both budesonide/formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the BID regimen (18.3 vs 9.6 L/minute; P<0.05). There were no between-group differences in nighttime awakenings due to asthma, or in the number and nature of adverse events.
Morice et al.[121] (2007) Budesonide-formoterol pMDI 160-4.5 µg vs budesonide-formoterol DPI 160-4.5 µg vs	DB, DD, MC, PG, RCT Outpatients ≥12 years of age with asthma for ≥6 months with inadequate control on an ICS alone, FEV_1 50 to 90% predicted normal, reversibility of >12% after inhalation of terbutaline 1 mg,	N=680 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, nighttime awakenings, asthma symptom score, symptom-free days and asthma control days	Primary: Patients in the budesonide/formoterol DPI and budesonide/formoterol MDI groups had improved morning PEF compared to those in the budesonide group by 31.4 and 28.6 L/minute, respectively (P<0.001). Secondary: Patients in the budesonide/formoterol groups had greater improvements observed compared to those in the budesonide group. End points were similar between the two budesonide/formoterol devices, with the exception of symptom-free and asthma control days, which were slightly improved with the DPI.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide pMDI 200 µg	and daily ICS use history ≥3 months			
Zetterström et al.[122] (2001) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 200 µg plus formoterol 4.5 µg, 2 inhalations BID (separate inhalers) vs budesonide 200 µg, 2 inhalations BID	DB, DD, MC, PG, RCT Adult patients with moderate persistent asthma (mean ICS dose 960 µg/day, mean predicted FEV_1 of 73.8%)	N=362 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, asthma control/symptoms, use of reliever medication, night-time awakenings, exacerbations, safety	Primary: Patients in the budesonide-formoterol and budesonide plus formoterol groups had greater improvements in morning PEF compared with those in the budesonide group (35.7 vs 32.0 s 0.2 L/min, respectively; P<0.001). Secondary: Evening PEF, total asthma symptom score, use of reliever medication, reliever use-free days, percentage of symptom-free days, percentage of asthma control days, and risk of mild exacerbations were all significantly improved in the budesonide-formoterol and budesonide plus formoterol groups compared with budesonide (P<0.01). No significant differences between treatment groups in night-time asthma awakenings or adverse events were observed.
Pohunek et al.[123] (2006) Budesonide-formoterol 80-4.5µg BID (fixed-dose inhaler) vs budesonide 200 µg BID and	AC, DB, MC, PG, RCT Patients 4 to 11 years of age with PEF >50% of predicted normal who had received stable treatment with an ICS, and history of an average of ≥1	N=630 12 weeks	Primary: Change in morning PEFR Secondary: Change from baseline in: evening PEF; total asthma-symptom score; night-time awakenings due to asthma symptoms;	Primary: The change in morning PEFR was significantly greater with budesonide/formoterol compared with budesonide (mean difference, 10.9 L/min; P<0.001). There was no significant difference in morning PEF between patients treated with budesonide/formoterol and those who received budesonide+formoterol in separate inhalers (P=0.14). Significantly greater changes in evening PEF were seen in patients treated with budesonide/formoterol compared to budesonide (mean difference, 9.1 L/min; P<0.001). There was no significant difference between budesonide/formoterol and budesonide+formoterol in separate inhalers.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
formoterol 9 µg BID (separate inhalers) vs budesonide 200 µg BID	clinically important exercise-induced bronchoconstriction per week during the 3 months leading up to the study		use of reliever medication; reliever-free days; symptom-free days; change in FEV_1, change in HRQOL (Pediatric AQLQ)	Patients treated with budesonide/formoterol had significantly greater changes in FEV_1 compared with budesonide (mean difference 0.078 L; P<0.001). There was no significant difference between budesonide/formoterol and budesonide+formoterol in separate inhalers. Asthma symptoms improved from baseline with all treatments, with no significant between-group differences. Overall PAQLQ(S) scores improved in all treatment groups, with adjusted mean changes of 0.437, 0.494 and 0.501 for the budesonide/ formoterol, budesonide+formoterol in separate inhalers and budesonide treatment groups, respectively. No significant between-group differences were observed. Scores were also improved for the individual domains, indicating improvements with regard to symptoms, emotional function and activity limitation; there were no differences between the treatment groups.
Pauwels et al.[124] (1997) FACET Budesonide 100 µg and formoterol 12 µg BID vs budesonide 400 µg and formoterol 12 µg BID vs budesonide 100 µg BID vs	DB, MC, PC, PG, RCT Adult patients with persistent asthma (mean ICS dose, 829 µg/day, mean predicted FEV_1 76%, mean reversibility of 21%)	N=852 1 year	Primary: Frequency of asthma exacerbations, lung function, asthma symptoms Secondary: Adverse events	Primary: The estimated yearly rates of severe asthma exacerbations were as follows: 0.34 for higher dose budesonide plus formoterol, 0.46 for those receiving higher dose budesonide, 0.67 for those receiving lower dose budesonide plus formoterol, and 0.91 for those receiving lower dose budesonide (P=0.01 for formoterol vs placebo, P<0.001 for lower vs higher dose of budesonide, no P value reported for lower dose budesonide plus formoterol vs higher dose budesonide plus placebo). The estimated yearly rates of mild asthma exacerbations were as follows: 13.4 for patients receiving higher dose budesonide plus formoterol, 22.3 for higher dose budesonide plus placebo, 21.3 for those receiving lower dose budesonide plus formoterol, and 35.4 for those receiving lower dose budesonide plus placebo (P<0.001 for formoterol vs placebo, P<0.001 for lower vs higher dose of budesonide, no P value reported for lower dose budesonide plus formoterol vs higher dose budesonide plus placebo). Secondary: All treatments were well tolerated throughout the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide 400 µg BID				
Kerwin et al.[125] (2009) Budesonide-formoterol 80-4.5 µg, 2 inhalations BID (320-18 µg/day) vs budesonide-formoterol 160-4.5 µg, 2 inhalations QPM (320-9 µg/day) vs budesonide-formoterol 80-4.5 µg, 2 inhalations QPM (160-9 µg/day) vs budesonide 160 µg, 2 inhalations QD (320 µg-day) All patients discontinued their current asthma therapy and	AC, DB, PG, RCT Patients ≥12 years of age with asthma for ≥6 months, mild to moderate asthma based on pulmonary function and ICS use, received an ICS or ICS/LABA therapy for ≥4 weeks before screening, with a FEV_1 60 to 90% and demonstrated reversibility of FEV_1 ≥12% and ≥0.20 L from baseline within 15 to 30 minutes of SABA use	N=619 12 weeks	Primary: Evening pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF, daytime and nighttime asthma symptom scores, daytime and nighttime rescue medication use, nighttime awakenings due to asthma, symptoms-free days, awakening-free nights, asthma control days, rescue medication-free days, patient withdrawals due to predefined criteria for worsening asthma, AQLQ, and safety	Primary: Budesonide-formoterol QD (320-9 µg/day) was significantly more effective than budesonide for evening pre-dose FEV_1 and evening PEF (P≤0.004). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (320-9 µg/day) (P<0.001). Mean morning PEF was maintained throughout the study with budesonide/formoterol QD (320-9 µg/day). Budesonide-formoterol QD (160-9 µg/day) was significantly more effective than budesonide in maintaining evening pre-dose FEV_1 and morning PEF during treatment (P≤0.016). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (160/9 µg/day) (P<0.001). Across all efficacy variables, differences between the two combination therapy QD groups were small and of questionable clinical relevance. The only significant difference noted between the two groups was for evening pre-dose PEF (LS mean difference, 0.05 L; 95% CI, 0.00 to 0.10) which favored the higher dose QD group (320-9 µg/day) (P=0.031). Secondary: Results for morning and evening pre-dose PEF are reported in the primary outcome section. Changes in rescue medication use and symptom-related variables significantly favored budesonide-formoterol QD (320-90 µg/day) vs budesonide (P≤0.045), except awakening-free nights, asthma control days and daytime rescue medication use. For combination therapy, QD administration (320-9 µg/day) and BID administration were similarly effective for diary variables reflective of the 12 hour period after evening dosing (nighttime asthma symptoms, awakening-free nights and nighttime rescue medication use), with significantly more favorable results for BID administration compared to QD administration (320-9 µg/day) for all other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
received SB budesonide/ formoterol 80-4.5 µg, 2 inhalations BID via MDI during a 4 to 5 week run-in period.				symptom-related and rescue medication use variables. Changes in symptom-related variables were significantly more favorable for budesonide-formoterol QD (160-9 µg/day) compared to budesonide (P≤0.023), except symptom-free days and daytime rescue medication use. For combination therapy, BID administration was significantly more effective than QD (160-9 µg/day) administration for all symptom-related and rescue medication use variables (P<0.01), except those that reflected the 12 hour period after evening dose. For combination therapy, results for asthma control days significantly favored BID administration compared to QD administration (320-9 and 160-9 µg/day) (P≤0.005). The percentages of patients withdrawing due to worsening asthma were as follows: 4.6, 6.6, 3.3 and 6.6% for budesonide-formoterol QD (320/9 µg/day), budesonide-formoterol QD (160-9 µg/day), budesonide/formoterol BID and budesonide (P values not reported). Mean changes in AQLQ overall and domain scores were small in all groups and less than the clinically meaningful difference. These changes were significantly more favorable for budesonide-formoterol BID vs budesonide (P≤0.018), but similar among the combination groups (except for the AQLQ symptoms domain, which significantly favored BID administration vs QD [160-9 µg/day] administration; P=0.034). All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity.
Corren et al.[126] (2007) Budesonide-formoterol pMDI 80-4.5 µg, 2 inhalations BID vs	DB, DD, MC, PC, RCT Patients ≥12 years of age with predominantly mild to moderate persistent asthma treated with an ICS	N=480 12 weeks	Primary: Changes from baseline in morning pre-dose FEV_1 and 12-hour mean FEV_1 after morning dose Secondary:	Primary: The mean change from baseline in pre-dose FEV_1 was greater in patients who received budesonide-formoterol compared to those who received budesonide, formoterol or placebo (P<0.005). Observed mean changes from baseline in 12-hour FEV_1 were greater in patients who received budesonide/formoterol compared to those who received budesonide or placebo (P<0.001). There was no evidence of diminution of the 12-hour bronchodilatory effect of budesonide-formoterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs placebo	for ≥4 weeks before screening and with a pre bronchodilator FEV_1 60 to 90% of predicted normal on ICS at screening		Morning and evening pre-dose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma	during the study period. Secondary: Patients who received treatment with budesonide/formoterol had greater mean increases from baseline in morning and evening pre-dose PEF compared to budesonide or formoterol (P<0.001). Mean decreases in symptom scores were greater with budesonide-formoterol compared to formoterol and placebo (P<0.046). Active treatments were associated with greater mean increases in awakening-free nights compared to placebo (P<0.012). Patients who received budesonide/formoterol had a greater mean reduction from baseline in daily rescue medication use compared to formoterol (P=0.006). The percentage of patients experiencing worsening asthma was reduced with budesonide-formoterol compared to formoterol or placebo (P≤0.01).
Murphy et al.[127] (2008) Budesonide-formoterol pMDI 80-4.5 µg, 2 inhalations BID vs budesonide pMDI* 80 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID	DB, DD, MC, PC, RCT Patients ≥18 years of age with predominantly mild to moderate persistent asthma	N=405 12 weeks	Primary: AQLQ, MOS Sleep Scale, asthma control variables (daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, percentage of asthma control days), and PSAM Secondary: Not reported	Primary: A significantly greater improvement from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores and asthma control variables was seen in the budesonide-formoterol group compared to placebo (P<0.033). A significantly greater improvement from baseline in AQLQ overall and domain scores, daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days and percentage of asthma control days was seen in the budesonide-formoterol group compared to formoterol (P<0.042). Significantly greater PSAM scores were reported in the budesonide-formoterol group compared to all other treatment arms (P<0.004). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Noonan et al.[128] (2006) Budesonide-formoterol pMDI 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide pMDI* 160 µg, 2 inhalations plus formoterol DPI 4.5 µg, 2 inhalations, both BID (separate inhalers) vs budesonide pMDI* 160 µg, 2 inhalations BID vs formoterol DPI 4.5 µg, 2 inhalations BID vs	DB, DD, MC, PC, RCT Patients ≥12 years of age, documented diagnosis of asthma for ≥6 months, moderate to high ICS use for ≥4 weeks, pre bronchodilator FEV_1 45 to 85% of predicted normal	N=596 12 weeks	Primary: Mean change from baseline in morning pre-dose FEV_1 and mean change from baseline in 12-hour FEV_1 after administration of morning dose Secondary: PEF, asthma symptoms, rescue medications use, and worsening asthma	Primary: Greater improvements in morning pre-dose FEV_1 were obtained in patients treated with budesonide-formoterol (0.19 L) than those treated with budesonide (0.10 L), formoterol (-0.12 L) or placebo (-0.17 L; P≤0.049). Patients who received budesonide-formoterol also demonstrated a greater improvement in 12-hour FEV_1 than budesonide, formoterol and placebo at two weeks and end of treatment (P≤0.001). Fewer patients receiving budesonide/formoterol than the individual products or placebo met worsening asthma criteria. Secondary: Budesonide-formoterol treatment resulted in greater improvements in morning and evening PEF, daytime and nighttime symptoms, worsening asthma and percentage of symptom-free days than budesonide, formoterol and placebo (P≤0.05). Patients receiving budesonide-formoterol demonstrated reduction in asthma symptoms, use of rescue medication and improvement in PEF within the first day and effects were maintained over the course of the 12-week study. Significant reductions in the use of rescue medication were observed in patients with budesonide-formoterol treatment compared to formoterol (P<0.001) and placebo but not with budesonide (P=0.066). Awakenings due to asthma were not significantly different between active treatment groups. Similar results were obtained for treatment arms with combination budesonide-formoterol and concurrent administration of the individual components. No clinically significant differences in adverse events were observed between treatment groups. Patients who received budesonide-formoterol had clinically significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				bronchodilation, defined as >15% improvement in FEV_1, within 15 minutes and effect was maintained over 12 hours.
Chervinsky et al.[129] (2008) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (fixed-dose inhaler) vs budesonide 160 µg and formoterol 4.5 µg, 2 inhalations BID (separate inhalers) vs budesonide 160 µg, 2 inhalations BID vs formoterol 4.5 µg, 2 inhalations BID vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with moderate to severe persistent asthma for ≥6 months	N=553 12 weeks	Primary: Asthma Quality of Life Questionnaire Secondary: Medical Outcomes Study Sleep Scale, PSAM questionnaire, diary variables	Primary: Mean AQLQ overall scores were 5.71 for budesonide-formoterol, 5.80 for budesonide plus formoterol, 5.35 for budesonide, 5.08 for formoterol, and 4.98 for placebo. Mean AQLQ(S) overall scores improved from baseline to end of therapy in all treatment groups except for the formoterol and placebo groups. Mean improvements from baseline to end of treatment in AQLQ overall scores were significantly greater for patients receiving budesonide-formoterol compared to those receiving budesonide (P<0.047), formoterol (P<0.001), or placebo (P<0.001). There was no significant difference between budesonide-formoterol and budesonide plus formoterol in any outcome. Secondary: No significant differences were observed among the treatment groups for the Medical Outcomes Study Sleep Scale scores. Patients receiving budesonide-formoterol reported awakening with shortness of breath or headache significantly less often than patients receiving formoterol (P=0.009) or placebo (P<0.001). Mean PSAM scores for control relief, perception of medication, and comparison with other medications at end of therapy were significantly higher in patients receiving budesonide-formoterol compared to those receiving budesonide, formoterol, or placebo (all, P≤0.001). A greater percentage of patients receiving budesonide-formoterol reported higher satisfaction ratings for items in the control relief index, the perception of medication index, and the comparison with other medication index than patients receiving budesonide, formoterol, or placebo. Patients receiving budesonide-formoterol experienced greater improvements in daily asthma symptom scores, daily rescue medication use, and the percentages of symptom-free days, rescue medication-free

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				days, and asthma control days compared to patients receiving budesonide, formoterol, or placebo (all P≤0.004). Patients reporting improvements in overall health at end of therapy was significantly higher in the budesonide-formoterol group (58.9%) compared to the formoterol (40.2%; P=0.01) and placebo (12.9%; P<0.001) groups. The percentage of patients reporting easier management of their asthma during treatment was significantly higher in the budesonide-formoterol group (61.7%) compared to the budesonide (46.2%; P=0.03) and placebo (19.4%; P<0.001) groups.
Beasley et al.[130] (2019) Budesonide-formoterol (200-6 µg, one inhalation through a Turbuhaler as needed) (budesonide-formoterol group) vs albuterol (100 µg, two inhalations from a pressurized metered-dose inhaler as needed for asthma symptoms) (albuterol group); vs budesonide (200 µg, one inhalation	MC, OL, RCT Patients 18 to 75 years of age with mild asthma (SABA as the sole asthma therapy in the previous three months and patient report of the use of the SABA on at least two occasions, but on an average of two or fewer occasions per day, in the previous four weeks)	N=668 52 weeks	Primary: Annualized rate of asthma exacerbations per patient Secondary: Number of exacerbations, time to the first exacerbation, number of severe exacerbations	Primary: The asthma exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (absolute rate per patient per year, 0.195 vs 0.400; relative rate, 0.49; 95% CI, 0.33 to 0.72; P<0.001) and did not differ significantly from that in the budesonide maintenance group (absolute rate per patient per year, 0.195 in the budesonide–formoterol group vs 0.175 in the budesonide maintenance group; relative rate, 1.12; 95% CI, 0.70 to 1.79; P=0.65). Secondary: The risk of exacerbation in the budesonide–formoterol group was lower than that in the albuterol group, as assessed in a time-to-first-event analysis (HR, 0.46; 95% CI, 0.29 to 0.73) and did not differ significantly from that in the budesonide maintenance group (HR, 0.93; 95% CI, 0.55 to 1.57). The number of severe exacerbations in the budesonide–formoterol group was lower than the number in both the albuterol group (9 vs 23; relative risk, 0.40; 95% CI, 0.18 to 0.86) and the budesonide maintenance group (9 vs 21; relative risk, 0.44; 95% CI, 0.20 to 0.96).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
through a Turbuhaler BID) plus as-needed albuterol (budesonide maintenance group)				
Hardy et al.[131] (2019) PRACTICAL Reliever therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler (one inhalation as needed for relief of symptoms) vs maintenance budesonide 200 µg Turbuhaler (one inhalation twice daily) plus terbutaline 250 µg Turbuhaler (two inhalations as needed)	MC, OL, PG, RCT Adults 18 to 75 years of age with a self-reported doctor's diagnosis of asthma who were using SABA for symptom relief with or without maintenance low to moderate doses of inhaled corticosteroids in the previous 12 weeks	N=885 52 weeks	Primary: Number of severe exacerbations per patient per year Secondary: Time to first severe exacerbation, combined moderate and severe asthma exacerbation rate, safety	Primary: The rate of severe asthma exacerbations was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline therapy (absolute rate per patient per year, 0.119 vs 0.172; relative rate, 0.69; 95% CI, 0.48 to 1.00; P=0.049). Secondary: Time to first severe exacerbation was longer with budesonide–formoterol than budesonide maintenance plus as-needed terbutaline. The number of severe exacerbations resulting in an emergency department visit or hospital admission was five and zero, respectively, with as-needed budesonide-formoterol and seven and two, respectively, with budesonide maintenance plus as-needed terbutaline. The combined moderate and severe asthma exacerbation rate was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline (absolute rate per patient per year, 0.165 vs 0.237; relative rate, 0.70; 95% CI, 0.51 to 0.95; P=0.024). Time to first moderate or severe exacerbation was longer with as-needed budesonide–formoterol than budesonide maintenance. The number of patients who were withdrawn because of treatment failure did not differ between groups (nine in the budesonide–formoterol group vs 11 in the budesonide maintenance plus terbutaline group; relative risk, 0.84; 95% CI, 0.35 to 2.00; P=0.69). Nasopharyngitis was the most common adverse event in both groups, occurring in 35% of patients receiving as-needed budesonide–formoterol and 32% of receiving maintenance budesonide plus terbutaline. The number of participants with at least one adverse event was 385 (88%) in the budesonide–formoterol group and 371 (83%) in the budesonide–

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				maintenance plus terbutaline group. There were two hospital admissions due to asthma in the budesonide maintenance group. There were no deaths in the study.
Bateman et al.[132] (2018) Budesonide–formoterol therapy with budesonide 200 µg–formoterol 6 µg Turbuhaler (one inhalation as needed for relief of symptoms) vs maintenance budesonide 200 µg Turbuhaler (one inhalation twice daily) plus terbutaline 0.5 mg Turbuhaler (as needed)	DB, MC, RCT Patients ≥12 years of age with mild asthma assessed as needing GINA step 2 treatment (regular, low-dose inhaled glucocorticoid)	N=4,176 52 weeks	Primary: To evaluate whether budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy in terms of the annualized rate of severe exacerbations Secondary: Time to the first severe exacerbation, use of inhaled and systemic glucocorticoids, FEV_1 before bronchodilator use, trial-specific asthma-related discontinuation, use of maintenance therapy and as-needed reliever therapy, the percentage of reliever-free days	Primary: Budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy with regard to the annualized rate of severe asthma exacerbations; the rate was 0.11 (95% CI, 0.10 to 0.13) in the budesonide–formoterol group and 0.12 (95% CI, 0.10 to 0.14) in the budesonide maintenance group. The rate ratio between the budesonide–formoterol group and the budesonide maintenance group was 0.97 (one-sided 95% upper confidence limit, 1.16). Secondary: A similar number of patients in each treatment group had severe exacerbations that led to an emergency department visit or hospitalization. The median daily metered dose of inhaled glucocorticoid was lower in the budesonide-formoterol group (66 µg) than in the budesonide maintenance group (267 µg). The time to the first exacerbation was similar in the two groups (HR, 0.96; 95% CI, 0.78 to 1.17). The change from baseline in the FEV_1 both before and after bronchodilator use was less in the budesonide–formoterol group than in the budesonide maintenance group (mean difference in FEV_1 before bronchodilator use, −32.6 ml [95% CI, −53.7 to −11.4]; mean difference in FEV_1 after bronchodilator use, −23.1 ml [95% CI, −41.9 to −4.2]). Fewer patients in the budesonide–formoterol group than in the budesonide maintenance group used more than eight inhalations of the as-needed agent per day (10.4% vs. 15.0%) or more than 12 inhalations per day (4.1% vs. 7.4%) at least once.
O'Byrne et al.[133] (2018)	DB, MC, RCT	N=3,836	Primary: To show that	Primary: Budesonide–formoterol used as needed was superior to terbutaline used as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol (200-6 µg) used as needed plus twice-daily placebo (budesonide-formoterol group) vs terbutaline used as needed plus twice-daily budesonide (200 µg) (budesonide maintenance group) vs terbutaline (0.5 mg) used as needed plus twice-daily placebo (terbutaline group)	Patients ≥12 years of age with mild asthma assessed as needing GINA step 2 treatment (regular, low-dose inhaled glucocorticoid)	52 weeks	budesonide–formoterol used as needed was superior to terbutaline used as needed in terms of asthma symptom control, measured according to the electronically recorded weeks with well-controlled asthma Secondary: Showing the noninferiority of budesonide–formoterol used as needed to budesonide maintenance therapy with regard to electronically recorded weeks with well-controlled asthma and comparing the rates and time to the first severe exacerbation and the rates and time to the first moderate-to-severe exacerbation in the budesonide–formoterol group	needed with regard to the primary outcome of the mean percentage of electronically recorded weeks with well-controlled asthma per patient (34.4% vs 31.1% of weeks; OR, 1.14; 95% CI, 1.00 to 1.30; P=0.046). Thus, the odds of having a week with well-controlled asthma during the 52-week trial period were 14% higher in the budesonide–formoterol group than in the terbutaline group. Secondary: Budesonide–formoterol used as needed was inferior to budesonide maintenance therapy with regard to the percentage of electronically recorded weeks with well-controlled asthma per patient (34.4 vs 44.4%; OR, 0.64; 95% CI, 0.57 to 0.73). Budesonide–formoterol used as needed resulted in a 64% lower rate of severe exacerbations than terbutaline used as needed (annualized exacerbation rate, 0.07 vs 0.20; rate ratio, 0.36; 95% CI, 0.27 to 0.49). The rates of severe exacerbations in the budesonide–formoterol group and the budesonide maintenance group did not differ significantly (annualized exacerbation rate, 0.07 and 0.09, respectively; rate ratio, 0.83; 95% CI, 0.59 to 1.16). Budesonide–formoterol used as needed also resulted in a 60% lower rate of moderate-to-severe exacerbations than terbutaline used as needed (0.14 vs. 0.36), but the rate in the budesonide–formoterol group did not differ significantly from that in the budesonide maintenance group (rate ratio, 0.95; 95% CI, 0.74 to 1.21). Budesonide–formoterol used as needed prolonged the time to the first severe exacerbation, as compared with terbutaline used as needed (HR, 0.44; 95% CI, 0.33 to 0.58). The results in the budesonide–formoterol group did not differ significantly from those in the budesonide maintenance group (HR, 0.90; 95% CI, 0.65 to 1.24). More patients in the terbutaline group had asthma-related discontinuations than did those in the budesonide–formoterol group or the budesonide maintenance group (1.6% vs 0.3% and 0.5%, respectively). The HR for the risk of asthma-related discontinuation in the trial was 0.18 (95% CI, 0.06 to 0.52) in the budesonide–formoterol group versus the terbutaline group and 0.66 (95% CI, 0.19 to 2.35) in the budesonide–formoterol group versus the budesonide maintenance group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			versus the terbutaline group and versus the budesonide maintenance group	
Gappa et al.[134] (2009) Fluticasone propionate 200 µg BID vs salmeterol-fluticasone propionate 50-100 µg BID (SFC)	DB, MC, PG, RCT Patients 6 to 14 years of age with persistent asthma uncontrolled by standard ICS doses	N=283 8 weeks	Primary: Change in mean morning PEF, asthma symptom scores, number of days without asthma symptoms, use of rescue albuterol, asthma control, and exacerbations Secondary: Not reported	Primary: Mean increase in morning PEF was 30.4 L/min in SFC group and 16.7 L/min in fluticasone propionate group. The mean improvement from baseline in morning PEF was significantly larger after SFC (8.6 L/min, 95% CI, 1.3 to infinity). Patients in the SFC group experienced more days without asthma symptoms (8.7%; 95% CI, 1.2 to 16.3) and more days without albuterol use (8.0%; 95% CI, 0.6 to 15.3) than patients receiving fluticasone propionate. Good asthma control was achieved for a longer period in SFC group (3.4 weeks) than in the fluticasone propionate group (2.7; P=0.02). Asthma exacerbations were recorded in three and six patients receiving SFC and fluticasone propionate, respectively. Both treatments were generally well tolerated. Serious adverse events were reported in two and one patients in the SFC and fluticasone propionate groups, respectively. Secondary: Not reported
Vaessen-Verberne et al.[135] (2010) Fluticasone propionate 200 µg, BID vs	DB, MC, PG, RCT Patients 6 to 16 years of age with asthma who are still symptomatic on conventional doses of ICSs	N=158 26 weeks	Primary: Percentage of symptom-free days during the last 10 weeks of treatment Secondary: Not reported	Primary: The percentage of symptom-free days did not differ between the two treatment groups in any of the treatment periods (zero to six, six to 16 and 16 to 26 weeks). The mean adjusted difference in symptom-free days between fluticasone propionate and combination therapy during the last 10 weeks was 2.6% (95% CI, -8.1 to 13.4; P=0.63) in the per-protocol analysis and 0.4% (95% CI, -9.1 to 9.9; P=0.93) in the intent-to-treat analysis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate - salmeterol 100/50 µg, BID All patients received fluticasone propionate 100 µg BID during a 4 week run-in period. A SABA was used for symptom relief during this period.				Secondary: Not reported
Strand et al.[136] (2004) Fluticasone propionate - salmeterol 100-50 µg BID vs fluticasone propionate 100 µg BID	DB, MC, PG, RCT Patients 23 to 54 years of age with persistent asthma who were using short acting bronchodilators one or more times per week for asthma for symptom relief	N=150 24 weeks	Primary: Percentage of symptom free days and nights Secondary: Morning and evening PEF, daytime symptom score, nighttime symptom score, days and nights without symptoms, β-agonist use, episode free days and night, and asthma exacerbations	Primary: Statistically significant increase in percentage of symptom free days and nights in fluticasone propionate -salmeterol group compared to fluticasone propionate group (P=0.008). Secondary: Statistically significant improvement in morning PEF (P=0.0011) and evening PEF (P=0.011) in the fluticasone propionate -salmeterol group compared to fluticasone propionate group. Statistically significant improvement in percentage of episode-free days and nights in the fluticasone propionate -salmeterol group compared to fluticasone propionate group (P=0.015). Statistically significant increase in percentage of days and nights without β-agonist use in the fluticasone propionate -salmeterol group compared to fluticasone propionate group (P<0.05). No statistically significant difference observed in asthma exacerbations between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bateman et al.[137] (2004) Fluticasone propionate -salmeterol 100-50 µg BID vs fluticasone propionate 100 µg BID NOTE: all patients were "stepped up" every 12 weeks until asthma totally controlled or highest dose reached (fluticasone propionate -salmeterol 500-50 µg BID or fluticasone propionate 500 µg BID)	DB, MC, PG, RCT Patients ≥12 years of age with asthma	N=3,421 12 months	Primary: Asthma control, symptoms, and rescue albuterol use Secondary: Dose of ICS, exacerbations	Primary: In the fluticasone propionate -salmeterol group, 71% of the patients achieved well-controlled asthma compared to 65% with the fluticasone propionate group. Compared to fluticasone propionate, individuals in the fluticasone propionate -salmeterol group were significantly faster to achieve asthma control ($P \leq 0.002$). Secondary: At a lower corticosteroid dose with fluticasone propionate -salmeterol, control was achieved more rapidly than fluticasone propionate alone. There were a significantly lower amount of exacerbations requiring oral corticosteroids and or hospitalizations or emergency visits in the fluticasone propionate -salmeterol group in each stratum ($P \leq 0.009$).
Bateman et al.[138] (2006) Fluticasone propionate -salmeterol 100-50 µg BID vs	DB, MC, PG, RCT Patients 12 to 80 years of age with asthma who were treated with only a β-agonist over the last 6 months, ≤10 pack year smoking	N=484 12 weeks	Primary: Mean morning PEF Secondary: Asthma control, symptoms, and rescue albuterol use	Primary: Patients in the fluticasone propionate -salmeterol group maintained the improved PEF values achieved in the OL treatment period compared to those in the fluticasone propionate group, whose PEF values decreased. The difference between the groups (63 L/min) was statistically significant ($P<0.001$). Secondary: Portion of patients with well controlled asthma remained higher in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate 250 µg BID NOTE: all patients were stabilized on fluticasone propionate - salmeterol 250-50 µg BID during OL treatment for 12 weeks and were "stepping down" therapy	history, FEV_1 of between 60 to 80% predicted value, demonstrated reversibility in lung function, combined daytime and nighttime symptom scores of ≥2 on ≥4 of the last 7 days of the run-in period and no exacerbations in the run-in period; patients received 12 weeks of OL fluticasone propionate plus salmeterol 250-50 µg BID before being randomized to the other treatment groups			fluticasone propionate -salmeterol group compared with the fluticasone propionate group (no P value reported). The odds of a patient achieving total control of their asthma were 62% greater in fluticasone propionate -salmeterol group compared to the fluticasone propionate group (P=0.017). Statistically significant difference in daytime symptom score, daytime and nighttime rescue use, and percent symptom free and rescue-free days and nights seen in favor of fluticasone propionate -salmeterol (P<0.05).
de Blic et al.[139] (2009) Fluticasone propionate - salmeterol 100-50 µg BID vs fluticasone propionate 200 µg BID	DB, MC, RCT Patients 4 to 11years of age with asthma who were previously uncontrolled on a low dose inhaled ICS (equivalent to beclomethasone 400 µg/day)	N=321 12 weeks	Primary: Change in mean PEF, asthma control, percent rescue free days, percent symptom free days, nighttime awakenings Secondary: Not reported	Primary: Change from baseline in mean morning PEF increased following both treatments, but was significantly greater in the fluticasone propionate - salmeterol group compared with fluticasone propionate (P=0.012). There was no significant difference in time to 'well controlled' asthma status between each group. Mean pre-bronchodilator maximal-expiratory flow at 50% vital capacity and percentage rescue-free days showed significantly greater improvements in the fluticasone propionate -salmeterol group compared with fluticasone monotherapy. All other efficacy indices showed comparable improvements in each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group. Secondary: Not reported
Stempel et al.[140] (2016) VESTRI Fluticasone propionate and salmeterol 100/50 µg or 250/50 µg inhaled BID via DPI vs fluticasone 100 µg or 250 µg inhaled BID via DPI (fluticasone dose was selected based on pre-study asthma medication, C-ACT score, and exacerbation history)	AC, DB, MC, RCT Children 4 to 11 years of age requiring daily asthma medication and with a history of asthma exacerbations in the previous year but not within the 30 days prior to randomization	N= 6,208 26 weeks	Primary: First serious asthma-related event (death, endotracheal intubation, or hospitalization) and first severe asthma exacerbation that led to treatment with systemic glucocorticoids Secondary: Number of rescue therapy free days, the number of asthma-control days, and C-ACT scores	Primary: Serious asthma-related events occurred in 27 patients in the fluticasone-salmeterol group and in 21 patients in the fluticasone-only group (HR, 1.28; 95% CI, 0.73 to 2.27). All serious asthma-related events in both groups were hospitalizations. Non-inferiority of fluticasone-salmeterol compared to fluticasone-only was demonstrated (P=0.006) based upon the a priori criteria. A total of 265 patients (8.5%) in the fluticasone-salmeterol group and 309 (10.0%) in the fluticasone–only group had a severe asthma exacerbation requiring treatment with systemic glucocorticoids (HR, 0.86; 95% CI, 0.73 to 1.01). There was no apparent between-group difference in the number of patients who had a severe exacerbation in each of the age groups (4 to 6 years and 7 to 11 years). Secondary: The mean percentage of rescue therapy–free days was similar between the fluticasone-salmeterol group and the fluticasone–only group (83.0% and 81.9%, respectively). The mean percentage of days with asthma control was also similar between treatment groups (74.8% and 73.4%, respectively). The C-ACT scores showed that 53.1% of all patients had asthma controlled at baseline and that 88.1% of the patients in the fluticasone-salmeterol group and 88.5% of those in the fluticasone-alone group had asthma controlled at the end of the trial.
Stempel et al.[141] (2016) AUSTRI Fluticasone propionate and salmeterol 100/50 µg, 250/50 µg, or	AC, DB, MC, PRO, RCT Patients ≥12 years of age with moderate to severe persistent asthma and a severe asthma	N= 11,679 26 weeks	Primary: The first serious asthma-related event (death, endotracheal intubation, or hospitalization) and the first severe	Primary: Serious asthma-related events occurred a total of 36 times in 34 patients in the fluticasone-salmeterol group and a total of 38 times in 33 patients in the fluticasone only group (HR, 1.03; 95% CI, 0.64 to 1.66). The upper boundary of the CI did not exceed the pre-specified limit of 2.0. As such, fluticasone-salmeterol was shown to be non-inferior to fluticasone alone (P=0.003) for this endpoint based upon the a priori criteria.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500/50 µg inhaled BID via DPI vs fluticasone propionate 100 µg, 250 µg, or 500 µg inhaled BID via DPI (Patients were stratified to a dose of fluticasone propionate based on current asthma medications and level of asthma control)	exacerbation in the past year requiring systemic glucocorticoids or hospitalization		asthma exacerbation Secondary: Severe adverse events leading to study withdrawal	At least one severe asthma exacerbation was reported in 480 of 5834 patients (8%) in the fluticasone-salmeterol group and in 597 of 5845 patients (10%) in the fluticasone only group (HR, 0.79; 95% CI, 0.70 to 0.89; P<0.001 when age was included as a covariate). Secondary: Adverse events leading to withdrawal from a study treatment were reported in 165 of 5,834 patients (3%) in the fluticasone-salmeterol group and in 180 of 5,845 patients (3%) in the fluticasone only group.
Bateman et al.[142] (2001) Fluticasone propionate - salmeterol 50-25 µg, 2 inhalations BID (HFA) vs fluticasone propionate - salmeterol 100-50 µg, 1 inhalation BID (DPI) vs	DB, DD, PG, RCT Patients ≥12 years of age with diagnosis of reversible airway obstruction, smoking history of <10 pack-years, using ICSs (beclomethasone, budesonide or flunisolide at a dose of 400 to 500 µg/day or fluticasone propionate 200 to 250 µg/day) for ≥4	N=497 12 weeks	Primary: Mean morning PEF Secondary: Evening PEF, daytime and nighttime symptom scores, albuterol use, and clinic FEV_1 values	Primary: Mean morning PEF values were equivalent between the fluticasone propionate - salmeterol HFA and Diskus groups (P value not reported). There was a significant improvement in mean morning PEF values in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.001). Comparisons were not made between the fluticasone propionate - salmeterol Diskus and the fluticasone propionate CFC groups. Secondary: Mean evening PEF improved in all three groups compared to baseline with the greatest improvements seen in the fluticasone propionate -salmeterol HFA and Diskus groups, and the difference was significant in the fluticasone propionate and salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.001). The number of symptom free days and nights increased in all three

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate 50 µg, 2 inhalations BID (CFC)	weeks prior to randomization, mean morning PEF 50 to 85% of value measured after albuterol during the last 7 days of the run-in period, symptomatic for the last 7 days of the run-in period, taking albuterol ≤800 µg/day and FEV_1 >50% of predicted value			treatment groups. The proportion of symptom free days and nights were similar in the fluticasone propionate -salmeterol HFA and Diskus groups. The fluticasone propionate -salmeterol HFA group reported significantly more symptom free days compared to the fluticasone propionate CFC group (P=0.001). The fluticasone propionate -salmeterol HFA group reported more symptom free nights compared to the fluticasone propionate CFC group, but this difference was not significant (P=0.063). The increase in albuterol free days and nights was similar in the fluticasone propionate -salmeterol HFA and Diskus groups. The increase in albuterol free days and nights was significantly higher in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC group (P<0.033) for every assessment period except for weeks five through eight (P=0.093). Clinic FEV_1 values improved in all three treatment groups and the differences between groups was not significant (P value not reported).
Nelson et al.[143] (2003) Fluticasone propionate - salmeterol 88-42 µg (HFA) vs fluticasone propionate 88 µg (CFC) vs	DB, MC, PG, RCT Patients diagnosed with persistent asthma uncontrolled with an as-needed SABA alone	N=283 12 weeks	Primary: Area under the FEV_1 curve relative to baseline, withdrawal due to asthma exacerbation, and morning and evening PEF Secondary: Not reported	Primary: Morning pre-dose FEV_1 was significantly improved in the fluticasone propionate - salmeterol HFA group compared to the fluticasone propionate CFC and salmeterol CFC groups (P≤0.016). Fewer patients in the fluticasone propionate -salmeterol HFA group withdrew due to worsening of asthma compared to the fluticasone propionate CFC and salmeterol CFC groups (P=0.024). Morning and evening PEF values were significantly increased in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and salmeterol CFC groups at endpoint (P≤0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 42 µg (CFC)				
Lundback et al.[144] (2006) Fluticasone propionate - salmeterol 250-50 µg BID vs fluticasone propionate 250 µg BID vs salmeterol 50 µg BID	DB, PG, RCT Patients 18 to 70 years of age with mild to moderate asthma, symptoms ≥2 times/week and ≥1 of the following: airway hyper-responsiveness, diurnal variability in PEF ≥20% in >3 days during the last 14 days of the run-in, ≥30% difference between the highest and second highest PEF reading during any 7 days of the run-in or reversible increase ≥15% in FEV_1 or PEF after β_2-agonist administration	N=282 12 months	Primary: Number of patients requiring an increase in study medication Secondary: Number of patients experiencing ≥2 asthma exacerbations during 12 months, clinic lung function tests (FEV_1 and FVC), airway hyper-responsiveness, diary card data containing information on morning PEF, rescue medication use, and daytime and nighttime asthma symptom scores	Primary: Statistically significant lower percentage of patients in the fluticasone propionate - salmeterol group required an increase in study medication compared to fluticasone propionate and salmeterol monotherapy (P<0.001). Secondary: Statistically significant lower number of patients having ≥2 asthma exacerbations in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy (P<0.01) and salmeterol monotherapy groups (P<0.001). Statistically significant improvement in morning PEF values in the fluticasone propionate -salmeterol group compared to the fluticasone propionate and salmeterol monotherapy groups (P<0.001). Statistically significant improvement in FEV_1 (P<0.001) and FVC (P<0.05) from baseline in the fluticasone propionate -salmeterol group compared to the salmeterol monotherapy group. No statistically significant difference in FEV_1 or FVC from baseline in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy group (P value not reported). Statistically significant improvement in airway hyper-responsiveness in the fluticasone propionate -salmeterol group compared to the fluticasone propionate monotherapy (P<0.05) and salmeterol monotherapy groups (P<0.001). Statistically significant increase in symptom-free days in the fluticasone propionate -salmeterol group and the fluticasone propionate monotherapy group than in the salmeterol monotherapy group (P<0.05). Statistically significant increase in symptom-free nights in the fluticasone propionate - salmeterol group and the fluticasone propionate monotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				group than in the salmeterol monotherapy group (P<0.001). Statistically significant increase in rescue-medication-free days in the fluticasone propionate -salmeterol group and the fluticasone propionate monotherapy group compared to the salmeterol group (P<0.05). Rescue-medication-free nights was 100% for all treatment groups.
Nathan et al.[145] (2006) Fluticasone propionate -salmeterol 110-21 µg, 2 inhalations BID (HFA) vs fluticasone propionate 110 µg, 2 inhalations BID (CFC) vs salmeterol 21 µg, 2 inhalations BID (CFC) vs placebo	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration, history of an ICS ≥3 months with no change in regimen for ≥1 month prior to screening at the following daily doses: beclomethasone 378 to 840 µg, triamcinolone 900 to 1,600 µg, flunisolide 1,250 to 2,000 µg, fluticasone propionate 440 to	N=365 12 weeks	Primary: For fluticasone propionate -salmeterol HFA vs fluticasone propionate CFC: AUC of the 12-hour serial FEV_1 relative to baseline For fluticasone propionate -salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, asthma symptom scores, albuterol use, and nighttime	Primary: The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and placebo groups (P<0.001), and at week 12 when compared to the salmeterol CFC group (P≤0.020). There was a significantly greater improvement in morning pre-dose FEV_1 at endpoint in the fluticasone propionate -salmeterol HFA group compared to the improvements in the fluticasone propionate CFC and salmeterol CFC groups (P≤0.001). There was a significant decrease in morning pre-dose FEV_1 in patients in the placebo group (P≤0.001). Significantly fewer patients in the fluticasone propionate -salmeterol HFA group withdrew due to worsening of asthma compared to the salmeterol CFC and placebo groups (P<0.001). The difference was not significant when comparing the fluticasone propionate -salmeterol HFA group and the fluticasone propionate CFC group (P value not reported). Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.001). There was a significant improvement in asthma symptom scores in the fluticasone propionate -salmeterol HFA group compared to the placebo group (P<0.001), but the difference when compared to the fluticasone propionate CFC and the salmeterol CFC groups was not significant (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	660 µg of MDI or 400 to 600 µg of DPI or budesonide 800 to 1,200 µg		awakenings requiring albuterol use	There was a significant increase in the proportion of days with no asthma symptoms in the fluticasone propionate -salmeterol HFA group compared to the placebo group (P<0.001), but the difference when compared to the fluticasone propionate CFC and the salmeterol CFC groups was not significant (P value not reported). The number of nighttime awakenings decreased in the fluticasone propionate -salmeterol HFA group and increased in the fluticasone propionate CFC, salmeterol CFC and placebo groups, but only the difference between the fluticasone propionate -salmeterol HFA and placebo groups was statistically significant (P<0.001). There was a significant reduction in the need for albuterol use in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and placebo groups (P≤0.005), but there was no significant difference when compared to the salmeterol CFC group (P value not reported).
Pearlman et al.[146] (2004) Fluticasone propionate -salmeterol 44-21 µg, 2 inhalations BID (HFA) vs fluticasone propionate 44 µg, 2 inhalations BID (CFC) vs salmeterol 21 µg, 2	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration	N=360 12 weeks	Primary: For fluticasone propionate -salmeterol HFA vs fluticasone propionate CFC: AUC of the 12-hour serial FEV_1 relative to baseline For fluticasone propionate -salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the	Primary: At week 12, the average percent change in serial FEV_1 compared to baseline was significantly greater for fluticasone propionate -salmeterol HFA compared to fluticasone propionate CFC, salmeterol CFC and placebo (P≤0.007). The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC and placebo groups (P<0.001), and at week 12 only for the salmeterol CFC group (P=0.006). There was a significant improvement in morning pre-dose FEV_1 from baseline in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.0112). There were significantly fewer patients withdrawn due to worsening of asthma in the fluticasone propionate -salmeterol group compared to the salmeterol CFC and placebo groups (P<0.001). The difference was not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalations BID (CFC) vs placebo Patients were stratified into 2 groups based on asthma therapy at baseline: Group 1-history of an ICS ≥3 months with no change in regimen for ≥1 month prior to screening at the following daily doses: beclomethasone 252 to 336 µg, triamcinolone 600 to 800 µg, flunisolide 1,000 µg, fluticasone propionate 176 µg of MDI or 200 µg of DPI or budesonide 400 to 600 µg. Group 2-β_2-agonist use for only for 1 week prior to screening (ineligible if			study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, patient-rated asthma symptom scores, albuterol use, nighttime awakenings requiring albuterol, and AQLQ scores	significant when comparing the fluticasone propionate -salmeterol HFA group and the fluticasone propionate CFC group (P value not reported). Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.006). There was a significantly greater percentage of days without asthma symptoms in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P<0.001). There was a significant decrease in nighttime awakenings in patients in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.007). There was a significant reduction in the need for albuterol in the fluticasone propionate -salmeterol HFA group compared to the fluticasone propionate CFC, salmeterol CFC and placebo groups (P≤0.002). There were no results reported for AQLQ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treated with an ICS within last month).				
Chapman et al.[147] (1999) Fluticasone propionate - salmeterol 250-50 µg BID (fixed-dose inhaler) vs fluticasone propionate 250 µg and salmeterol 50 µg BID (separate inhalers)	DB, DD, RCT Individuals 13 to 75 years of age with symptomatic asthma	N=371 28 weeks	Primary: Change in PEFR Secondary: Mean daytime symptom score and FEV_1	Primary: Over weeks one to 12, PEFR was 43 L/minute for the combination therapy group and 36 L/minute for the concurrent therapy group respectively. The difference between the two treatment groups was 6 L/minute (CI, -13 to 0; P=0.114), which was within the predefined criteria for clinical equivalence. Secondary: Over weeks one to 12, 35% of the combination therapy group had a mean daytime symptom score of zero compared to 31% of the concurrent therapy group. No statistically significant difference in FEV_1 between the combination and concurrent therapy groups was noticed (P value not reported).
Nelson et al.[148] (2003) Fluticasone propionate - salmeterol 100-50 to 500-50 µg BID vs fluticasone propionate 100 to 500 µg BID and salmeterol 50 µg BID	MA (4 DB, DD, MC, RCTs) Individuals ≥4 years of age diagnosed with asthma	N=1,375 All trials were 12 weeks in duration	Primary: Change from baseline in mean PEF over 12 weeks Secondary: Mean change in evening PEF and clinic FEV_1, median percentage of symptom-free days, nights or both, and rescue inhaler free	Primary: A significant advantage (5.4 L/minute) was seen for PEF in the combination therapy over the 12 week treatment period (P=0.006). Secondary: There was a difference in favor of the combination therapy in the mean difference in FEV_1 (0.04 L) compared to the concurrent therapy (P=0.054). The difference was statistically significant (6.11 L/minute) in the mean evening PEF in favor of the combination therapy (P<0.001). There was no significant difference seen in the percentage of symptom-free and/or rescue inhaler free days and nights between treatment groups (P=0.165 and P=0.635).
You-Ning et al.[149] (2005) Fluticasone	MC, OL, PG, RCT Patients 18 to 70 years of age with	N=270 4 weeks	Primary: Morning PEF Secondary:	Primary: Morning PEF improved significantly in both the fluticasone propionate - salmeterol HFA and Diskus groups compared to baseline (P<0.05), but the differences between groups was not significant (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propionate - salmeterol 125-25 µg, 2 inhalations BID (HFA) vs fluticasone propionate-salmeterol 250-50 µg, 1 inhalation BID (DPI)	diagnosis of asthma, receiving stable doses of budesonide or beclomethasone up to 1,200 µg/day or fluticasone propionate up to 600 µg per/day for ≥1 month, or required therapy with ICSs, total score of ≥8 for daytime and nighttime symptoms and ≥15% reversibility and 200 mL elevation in FEV_1 following albuterol		Rescue medication use, daytime and nighttime symptom scores, evening PEF, FEV_1 and patient self-evaluation of efficacy	Secondary: All secondary endpoints improved significantly compared to baseline in both the fluticasone propionate -salmeterol HFA and Diskus groups ($P<0.05$), but the difference between groups was not significant for any secondary endpoint ($P>0.05$) except patient self-evaluation of efficacy at visit three which was significantly higher in the Diskus group compared to the HFA group ($P<0.05$).
Miller et al.[150] (2016) Fluticasone propionate and salmeterol 100/6.25 µg via MDPI vs fluticasone propionate and salmeterol 100/12.5 µg via MDPI vs	DB, MC, RCT, XO Patients ≥ 12 years of age with persistent asthma and a pre-dose maximum FEV_1 of 40 to 85% of predicted normal, ≥15% reversibility of FEV_1, acceptable and repeatable spirometry, a medium-dose ICS for ≥8 weeks, and maintained on a	N=72 5 weeks	Primary: Baseline-adjusted FEV_1 AUC over 12 hours (AUC_{0-12}) after medication dose Secondary: PK and tolerability	Primary: The FEV_1 AUC_{0-12} was significantly higher with all fluticasone propionate-salmeterol MDPI doses and the fluticasone propionate-salmeterol DPI dose as compared to the fluticasone propionate alone MDPI (P= 0.0001) The FEV_1 AUC_{0-12} was significantly higher with fluticasone propionate-salmeterol MDPI 100/50 versus fluticasone propionate-salmeterol 100/50 DPI (LS mean, 57.88 mL; 95% CI, 22.0 to 93.7; P=0.0017). The FEV_1 AUC_{0-12} values for fluticasone propionate-salmeterol MDPI 100/25 and fluticasone propionate-salmeterol MDPI 100/12.5 were higher than for fluticasone propionate-salmeterol 100/50 DPI; however, they did not achieve statically significance (LS mean, 34.14 mL; 95% CI, -1.8 to 70.1; P=0.0624 and LS mean, 3.42 mL; 95% CI, -32.3 to 39.1; P=0.8503 respectively). The FEV_1 AUC_{0-12} was lower with fluticasone propionate-salmeterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate and salmeterol 100/25 µg via MDPI vs fluticasone propionate and salmeterol 100/50 µg via MDPI vs fluticasone propionate 100 µg via MDPI vs fluticasone propionate and salmeterol 100/50 µg via DPI (In this XO study, patients received each of the study medications once in the AM with a five to seven-day washout between treatments. During the washout periods, patients received	stable ICS dose for ≥4 weeks.			MDPI 100/6.25 versus fluticasone propionate-salmeterol 100/50 DPI. Secondary: The salmeterol AUC from time 0 to the time of the last measurable concentration (AUC_{0-t}) for fluticasone propionate-salmeterol MDPI 100/12.5 and 100/25 was lower versus fluticasone propionate-salmeterol DPI 100/50. The salmeterol AUC_{0-t} for fluticasone propionate-salmeterol MDPI 100/50 was higher than for fluticasone propionate-salmeterol DPI 100/50. All fluticasone propionate-salmeterol MDPI doses were generally well tolerated. The percentage of patients with one or more adverse events was lowest in the fluticasone propionate MDPI 100 group and the fluticasone propionate-salmeterol MDPI 100/6.25 group (3% and 4%, respectively). The percentage of patients with one or more adverse events was similar in the fluticasone propionate-salmeterol MDPI 100/12.5, 100/25, and 100/50 groups and the fluticasone propionate/salmeterol DPI 100/50 group (9%, 9%, 7%, and 8%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate 50 µg BID via MDPI as maintenance therapy)				
Weinstein et al.[151] (2010) Mometasone-formoterol 200-10 to 400-10 µg BID (MF/F) vs mometasone 400 µg BID (MF) All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 400 µg, BID.	DB, MC, PG, RCT Patients ≥12 years of age with asthma for ≥12 months uncontrolled on high dose ICSs (>1,000 mg beclomethasone equivalent) with or without LABA for 12 weeks before screening	N=728 12 weeks	Primary: Mean change in FEV_1 $AUC_{0\ to\ 12h}$ for combination therapy (800-20 µg) vs mometasone Secondary: Change from baseline in ACQ, AQLQ, proportion on nocturnal awakenings requiring SABA rescue medication, trough FEV1, evening PEF and number of asthma deteriorations (any one of the following: ≤80% of baseline FEV_1, a ≤70% of baseline PEF for at least two consecutive days or a clinically judged deterioration resulting in emergency treatment, hospitalization, or	Primary: A significant improvement from baseline to week 12 for mean change in FEV_1 $AUC_{0\ to\ 12h}$ occurred with both doses of combination therapy compared to mometasone alone (4.19 and 3.59 L/hour vs 2.04 L/hour; for the combination therapy doses of 200-10 µg, 400-10 µg and mometasone 400 µg, respectively; P<0.001). Both doses of combination therapy resulted in rapid (five minutes) and sustained improvement in lung function throughout 12 weeks. Secondary: Both doses of combination therapy were associated with lower ACQ scores after 12 weeks of treatment compared to mometasone alone (P≤0.014), indicating an improvement in asthma control. The mean AQLQ scores increased in all three treatment groups indicating less impairment on activities; however, differences between the groups were not statistically significant. Both doses of combination therapy significantly reduced the number of nocturnal awakenings due to asthma that required SABA use compared to mometasone alone (P≤0.006). Mean changes from baseline to week 12 were 0.10, 0.14 and 0.19 L for mometasone 400 µg monotherapy, 200-10 µg combination therapy and 400-10 µg combination therapy, respectively. The 400-10 µg combination dose was significantly more effective at improving trough FEV_1 at week 12 (P=0.006) and at all other time points (P≤0.04) compared to monotherapy, whereas the 200-10 µg combination dose was more effective than monotherapy only at week 4 (P=0.027). The improvement from baseline in evening PEF was 11.8, 13.3, and 6.6% for the 200-10 µg and 400-10 µg combination doses, and 400 µg of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment with additional asthma medication such as systemic glucocorticoid steroids	monotherapy, respectively. Improvements from baseline in evening PEF were also significantly greater for both combination treatment groups compared to mometasone monotherapy at all time points (P≤0.004). Patients receiving the 200-10 µg dose of combination therapy had significantly fewer asthma deteriorations compared to the mometasone monotherapy group (P=0.038). The difference between the 400-10 µg combination treatment group and the mometasone monotherapy group was not significant (P=0.053). A combined analysis of both doses of (400-10 µg and 200-10 µg) showed that combination treatment was significantly better than mometasone monotherapy for reducing asthma deteriorations (P=0.029).
Nathan et al.[152] (2010) Mometasone-formoterol 100-5 µg, 2 inhalations BID (MF/F) vs mometasone 100 µg, 2 inhalations BID (MF) vs formoterol 5 µg, 2 inhalations BID (F) vs placebo	DB, MC, PC, PG, RCTC Patients ≥12 years of age with asthma for ≥12 months, who were on a stable asthma regimen for ≥2 weeks and with a history of medium-dose ICS use for ≥12 weeks, with or without additional LABA; patients also had FEV_1 of ≥12% or a volume increase of ≥200 mL after 15 to 20 minutes of albuterol-salbutamol administration or of a nebulized SABA, PEF	N=781 26 weeks	Primary: Time to first asthma deterioration Secondary: FEV_1 $AUC_{0–12h}$, trough FEV_1, PEF, asthma control, quality of life, asthma symptom scores, nocturnal awakenings, rescue medication use	Primary: There was a delay in time to first asthma deterioration with MF/F and MF compared to F and placebo (both P<0.001). The median times to first asthma deterioration were days 92 and 131 for those receiving F and placebo, respectively. Because <50% of the patients in the MF/F and MF groups experienced an asthma deterioration, median times to first asthma deterioration could not be determined. The proportion of patients experiencing asthma deteriorations was 30.4% with MF/F, 33.9% with MF, 54% with F, and 55.6% with placebo (P<0.001). Secondary: Mean FEV_1 $AUC_{0–12h}$ improved more with MF/F than with MF (P<0.001) or placebo (P<0.001) at all time points throughout the study and with F at week 12 (P<0.017). Trough FEV_1 showed significant improvement with MF/F vs F and placebo. Treatment with MF/F was significantly better than treatment with F after week 1 (P<0.001) and placebo at all time points (P<0.006). Treatment with MF/F was also statistically better than treatment with MF at several time points, including week 26 (P<0.023). The change from baseline in AM PEF was significantly greater for the MF/F group than for the other groups (P<0.008), and treatment with MF

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	variability of ≥20%, or a diurnal variation PEF of ≥20%			alone was statistically significant vs placebo (P<0.001). There was a significant improvement in asthma control for patients treated with MF/F vs F or vs placebo (P<0.001 for both). There was a significantly greater mean improvement in AQLQ(S) score between baseline and week 26 for MF/F vs F (P<0.001) and placebo (P=0.004). Mean improvement from baseline in AQLQ(S) score at week 26 was statistically significantly greater for MF vs F (P=0.039), but similar for MF and placebo (P=0.130). AQLQ(S) outcomes did not differ significantly for F vs placebo at any time point during treatment. The 24-hour asthma symptom scores were significantly improved in the MF/F group compared with both the F and placebo groups (P<0.001). Treatment with MF also showed significant improvements over both F and placebo (P<0.001). Both MF/F and MF groups exhibited greater changes for nocturnal wakenings due to asthma requiring the use of SABA vs F (MF/F; P<0.001, MF; P<0.001), and placebo (MF/F; P<0.001, MF; P<0.003). There was no significant difference between F and placebo. The 24-hour SABA use was significantly reduced in both the MF/F (-61.1%) and the MF (-22.1%) groups vs either the F (184.1%) or the placebo (79.1%) groups (P<0.001). The most common AEs were nasopharyngitis (MF/F, 6.3%; MF, 7.8%; F, 6.4%; placebo, 3.6%), upper respiratory tract infection (MF/F, 5.8%; MF, 8.3%; F, 5.9%; placebo, 8.7%), and headache (MF/F, 4.7%; MF, 5.2%; F, 3.0%; placebo, 3.6%).
Weinstein et al.[153] (2020) Mometasone furoate-formoterol 50-5 µg two puffs twice daily	DB, MC, PG, RCT Patients five to 11 years of age with a diagnosis of asthma ≥six months, FEV_1 % predicted >60%	N=181 26 weeks	Primary: Change from baseline in AM postdose % predicted FEV_1 as measured across 0 to 60 minutes	Primary: Treatment with mometasone furoate-formoterol led to a statistically significant overall treatment advantage of 5.21 percentage points (P<0.001) compared with mometasone furoate sustained across all study visits. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mometasone furoate 50 µg two puffs twice daily	to ≤90% postbronchodilator wash-out, stable dose of ICS/LABA for ≥4 weeks, demonstration of reversibility and able to discontinue previously prescribed asthma medication		postdose at 0, 5, 15, 30 and 60 minutes, averaged across day 1, week 1, week 3, week 8 and week 12 of treatment Secondary: Change from baseline in AM postdose %predicted FEV_1 as measured at 5, 15, 30 and 60 minutes, 2 hours, and 4 hours postdose on day 1 of treatment, safety	Significant improvement in the change from baseline AM postdose in % predicted FEV_1 was achieved with mometasone furoate-formoterol relative to mometasone furoate on day 1 at 5 minutes, which was sustained through 4 hours postdose (P<0.001). These rapid bronchodilatory effects were also observed at week 12. Approximately half (49.2%) of the participants reported one or more adverse events. There were fewer participants with adverse eventsin the mometasone furoate-formoterol group (40.7%) compared with the mometasone furoate group (57.8%).
Bateman et al.[154] (2003) Budesonide-formoterol 160-4.5 µg, 1 inhalation BID vs fluticasone propionate 250 µg, 1 inhalation BID	DB, DD, PG, RCT Patients with asthma (average age of 42 years, FEV_1 78% predicted, reversibility 21%)	N=373 12 weeks	Primary: Morning PEF Secondary: Evening PEF, clinic FEV_1, use of reliever medication, symptom-free days, asthma control days, night-time awakenings, and risk of having an exacerbation	Primary: Patients in the budesonide-formoterol group had significantly greater increases in morning PEF than those in the fluticasone propionate group (27.4 vs 7.7 L/minute, respectively; P<0.001). Secondary: Those in the budesonide-formoterol group had a significant improvement in their evening PEF and FEV_1 compared to the fluticasone propionate group (P values not reported). Also, patients in the budesonide-formoterol group utilized less reliever medication (P=0.04) and had a greater proportion of reliever-free days (P<0.001). Patients in the budesonide-formoterol group had a 32% risk reduction of having an exacerbation compared to those in the fluticasone propionate group (P<0.05). Although not statistically significant, patients in the budesonide-formoterol group had improvements in regards to symptom-free days,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				asthma control days and nighttime awakenings vs those in the fluticasone propionate group (60.4 vs 55.5%, 57.8 vs 52.4% and 7.9 vs 9.6%, respectively; P values not reported).
Ericsson et al.[155] (2006) Budesonide-formoterol 160-4.5 µg BID vs fluticasone propionate 250 µg BID	DB, DD, MC, PG, RT Patients ≥18 years of age with moderate-persistent asthma, diagnosis ≥6 months, on ICS (200 to 1,000 µg) ≥30 days, FEV_1 60 to 90% predicted normal, ≥12% reversibility after inhalation of terbutaline or salbutamol†	N=339 12 weeks	Primary: Morning PEF Secondary: Time to first exacerbation, asthma symptom score, rescue medication use	Primary: Patients in the budesonide-formoterol treatment group had a statistically significant greater improvement in morning PEF of 27.4 L/min in comparison to 7.7 L/min observed in the fluticasone propionate treatment group (19.7% difference; 95% CI, 13.6 to 25.9; P<0.001). Secondary: Patients in the budesonide-formoterol treatment group had a statistically significant greater increase in the time to first mild exacerbation in comparison to those in the fluticasone propionate treatment group (P=0.04). Budesonide-formoterol was associated with a greater reduction in the use of rescue medications in comparison to fluticasone propionate –0.31 inhalations/day vs –0.13 inhalations/day, respectively; P=0.04).
Akamatsu et al.[156] (2013) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID	AC, RCT Patients >18 years of age with asthma for ≥6 months who were able to perform expiratory maneuvers and were receiving fluticasone propionate -salmeterol for ≥8 weeks	N=66 12 weeks	Primary: ACQ5, pulmonary function tests and exhaled NO parameters Secondary: Not reported	Primary: There was no change in ACQ5 between patients treated with budesonide-formoterol and fluticasone propionate -salmeterol; however, the proportion of patients with an improvement in ACQ5 was significantly higher in the budesonide-formoterol group compared to the fluticasone propionate -salmeterol group (51.6 vs 16.7%; P=0.003). The minimum PEF and maximum PEF significantly improved (P=0.021 and P=0.0054, respectively) in patients treated with budesonide-formoterol but not for patients in the fluticasone propionate -salmeterol group; however, there was no significance between the two treatment groups overall (P=0.573 and P=0.092, respectively). The changes in exhaled NO parameters after 12 weeks of treatment demonstrated significant improvements in CANO (P=0.007) and CANOcorr (P=0.008) in the budesonide-formoterol group but not in the fluticasone propionate -salmeterol group. The differences between the treatment groups were statistically significant, favoring budesonide-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				formoterol (P=0.047 and P=0.037, respectively). Secondary: Not reported
Price et al.[157] (2007) Budesonide-formoterol 200-6 µg, 2 inhalations BID (adjustable maintenance dose) vs fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID (stable dose) During weeks 1 to 4, patients received either 1 inhalation of fluticasone propionate - salmeterol 250-50 µg BID or 2 inhalations of budesonide-formoterol 200-6 µg and during weeks 5 to 52, those who met the criteria, received budesonide/formot	DB, DD, MC, PG, RCT Outpatients 18 to 70 years of age, with a clinical asthma history, an FEV_1 60 to 90% predicted normal, had received an ICS dose equal to 200 to 500 µg/day of beclomethasone and LABA, or an ICS alone at dose equal to >500 to 1,000 µg beclomethasone (≥12 weeks prior to enrollment)	N=688 1 year	Primary: Symptom-free days (defined as symptom score of zero in a 24-hour period) Secondary: Rate of exacerbations	Primary: Patients in the fluticasone propionate -salmeterol group had a significantly greater percentage of symptom/free days (58.8%) over the entire year, compared to patients in the budesonide/formoterol group (52.1%; P=0.034). Secondary: The adjusted annual mean exacerbation rate was also significantly lower in the fluticasone propionate -salmeterol group compared to the budesonide/formoterol group (47%; P=0.008)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erol-AMD or fluticasone propionate - salmeterol-FD.				
Vogelmeier et al.[158] (2012) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via Turbuhaler SMART™ [plus additional inhalations as needed] vs fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID via Diskus [plus salbutamol as needed] Maintenance doses could be titrated by clinicians after the first four weeks.	PH, SA Asian outpatients ≥12 years of age with asthma for ≥6 months that used ≥500 µg/day of budesonide or fluticasone propionate (or ≥1,000 µg of another ICS) for ≥1 month prior to study entry, had pre-terbutaline FEV_1 40 to 90% of predicted and at least one severe exacerbation >2 weeks and ≤12 months before study start; patients also had used as-needed medications on ≥4 of the past 7 days of run-in	N=404 12 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit, the need for oral steroids ≥3 days or unscheduled visit leading to treatment change) Secondary: Asthma control (assessed using ACQ-5), quality of life (using AQLQ(S))	Primary: The time to the first severe exacerbation was significantly longer in patients treated with maintenance plus as-needed budesonide-formoterol compared to patients treated with fluticasone propionate -salmeterol plus as-needed salbutamol (230 vs 45 days; P=0.024). Patients treated with the adjusted budesonide-formoterol regimen had a 44% reduction in risk of a first exacerbation compared to patients treated with fluticasone propionate -salmeterol plus salbutamol (95% CI, 0.32 to 0.95; P=0.033). The rate of severe exacerbations was lower in the maintenance plus as-needed budesonide-formoterol treatment group (0.16/patient/year) compared to the fluticasone propionate -salmeterol plus salbutamol treatment group (0.26/patient/year) (RR, 0.62/patient/year; 95% CI, 0.41 to 0.94; P=0.024). Secondary: The mean changes in overall ACQ-5 scores for the maintenance plus as-needed budesonide-formoterol treatment group and the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group were -0.702 and -0.655, respectively, although this difference was not statistically significant. The mean change in overall AQLQ(S) scores for the maintenance plus as-needed budesonide-formoterol treatment group and the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group were 0.843 and 0.727, respectively, although this difference was not statistically significant. A total of 33 serious adverse events occurred, 14 in the maintenance plus as-needed budesonide-formoterol treatment group and 19 in the fluticasone propionate -salmeterol plus as-needed salbutamol treatment group. Headache occurred more frequently in the fluticasone propionate - salmeterol plus as-needed salbutamol treatment group compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				budesonide-formoterol treatment group (5 vs 2%; P=0.033). The most commonly reported adverse events included upper respiratory tract infections, nasopharyngitis, pharyngolaryngeal pain, headache and hoarseness. With the exception of headache, the rates of adverse events were similar in both groups.
Fitzgerald et al.[159] (2005) Budesonide-formoterol 200-6 µg BID via DPI vs salmeterol-fluticasone propionate 50-250 µg BID via DPI	DB, DD, RCT Individuals 18 to 70 years of age, with a documented clinical history of asthma and an FEV_1 between 60 to 90% of projected normal	N=706 1 year	Primary: Percentage of symptom-free days Secondary: Daily asthma symptom scores, morning PEF, percentage of days free of rescue medication use, and nighttime awakenings due to asthma	Primary: The percentage of symptom-free days was higher with fluticasone propionate -salmeterol compared to budesonide-formoterol (58.8 vs 52.1%; P=0.034). The percentage of symptom-free days was significantly higher with fluticasone propionate -salmeterol compared to budesonide-formoterol during weeks five through 52 (73.8 vs 64.9%; P=0.030). Secondary: In the fluticasone propionate -salmeterol group there was a significant difference in the adjusted annual mean exacerbation rate compared to the budesonide-formoterol group (0.18 vs 0.33; P=0.008). The median value for the percentage of days free of rescue medication over weeks five through 52 was 94.5% in the fluticasone propionate -salmeterol group compared to 90.7% in the budesonide-formoterol group (P=0.008). Over the 52-week treatment period the mean morning PEF was significantly higher in the fluticasone propionate -salmeterol group compared to the budesonide-formoterol group (400.1 vs 390.6 L/minute; P=0.006).
Ringdal et al.[160] (2002) EDICT Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation	DB, DD, PG, RCT Patients 16 to 75 years of age with a clinical history of reversible airway obstruction, symptomatic on	N=428 12 weeks	Primary: Mean morning PEF (during week 12 of treatment) Secondary: Morning and evening PEF, day	Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 to 386 L/minute with fluticasone propionate -salmeterol compared to an increase of 348 to 389 L/minute observed with budesonide-formoterol (-3.2 L/minute mean difference; 95% CI, -15.0 to 8.6; P=0.593). Similar results in mean morning PEF were seen in the intent-to-treat

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs budesonide 800 µg and formoterol 12 µg, 1 inhalation BID	1,000 to 1,600 µg/day of budesonide, beclomethasone or flunisolide, or 500 to 800 µg/day of fluticasone propionate, FEV_1 50 to 85%, increased symptom scores or reliever use		and nighttime symptom scores, nighttime awakenings, FEV_1, rate and severity of exacerbations, and use of rescue medication, withdrawals from study	population for both treatment groups. Secondary: The mean rate of exacerbation/patient/84 days of treatment was significantly lower in the fluticasone propionate -salmeterol group in comparison to the budesonide-formoterol group with a risk reduction of 36% (0.472 vs 0.735, respectively; 95% CI, 0.51 to 0.80; P<0.001). Over the entire treatment period, patients in the fluticasone propionate -salmeterol group had a statistically significant greater percentage of nights with no awakenings, without symptoms and a symptom score of <2 in comparison to those in the budesonide-formoterol group (P=0.02, P=0.04 and P=0.03, respectively). There was no significant difference in morning and evening PEF, clinic-measured FEV_1, improvement in day-time symptoms and use of relief medication (salbutamol) between the two treatment groups.
Bousquet et al.[161] (2007) Fluticasone propionate -salmeterol 500-50 µg, 1 inhalation BID via Diskus and terbutaline as needed vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID and as needed via DPI	DB, MC, PG, RCT Patients ≥12 years of age with symptomatic asthma, FEV_1 ≥50%, and had experienced an asthma exacerbation in the previous year	N=2,309 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration leading to hospitalization or emergency room visit or use of oral corticosteroids for ≥3 days) Secondary: Rate of severe exacerbations, risk of first hospitalization, rate of hospitalization, FEV_1, morning and	Primary: The time to first severe exacerbation was not statistically different between the treatment groups (HR, 0.82; P=0.12). Secondary: There was a 21% reduction in the overall exacerbation rate in the budesonide-formoterol group compared to the fluticasone propionate -salmeterol group (25 vs 31 events/100 patients/year). The difference between groups was significant (P=0.039). The risk of hospitalization or emergency room visit was decreased in the budesonide-formoterol group when compared to the fluticasone propionate -salmeterol group (HR, 0.64; P=0.031). There was a 31% reduction in the rate of hospitalization with budesonide-formoterol compared to fluticasone propionate -salmeterol (9 vs 13 events/100 patients/year; P=0.046). FEV_1 increased in both groups from 2.29 to 2.52 L in the budesonide-formoterol group and from 2.70 to 2.49 L in the fluticasone propionate -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			evening PEF, as needed medication utilization, asthma control days, symptom free days, and safety	salmeterol group. There was no difference between the treatments (P value not reported). Morning and evening PEF scores improved in both treatment groups (for budesonide-formoterol there was an increase from 330.1 to 359.5 L/minute in the morning PEF and an increase from 336.7 to 362.3 in evening PEF; for fluticasone propionate -salmeterol there was an increase from 329.0 to 359.4 in the morning PEF and an increase from 337.7 to 361.7 in the evening PEF; a difference that was not statistically significant (morning; P=0.67, evening; P=0.42 evening). Use of high number as needed medication inhalations of >4, >6 and >8 inhalations/day was reported in 29, 13 and 4% of patients using the fluticasone propionate -salmeterol treatment and in 27, 9 and 3% using the budesonide-formoterol treatment. The differences were not significant (P=0.36). Asthma control days increased in both treatment groups from 6.3 and 5.8% at baseline to 44.0 and 44.9% in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. The difference was not statistically significant (P=0.37). Symptom free days improved from 10.7 and 11.2 at baseline to 47.2 and 48.1 in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. The difference was not statistically significant (P=0.73). Adverse events were reported in 39 and 40% of patients in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. Serious adverse events were three percent in both groups. There were 11 and 20 patients who discontinued the study due to adverse events in the budesonide-formoterol and fluticasone propionate -salmeterol groups respectively. One death occurred in the study due to typhoid fever; however, it was not linked to the study medications.
Dahl et al.[162] (2006)	DB, MC, PG, RCT Patients with	N=1,391 24 weeks	Primary: Rate of exacerbations	Primary: There were no statistically significant differences in mean rate of exacerbations over 24 weeks, or severity of exacerbations observed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID vs budesonide-formoterol 200-6 µg, 2 inhalations BID	persistent asthma, currently receiving 1,000 to 2,000 µg/day of ICS, FEV_1 reversibility of ≥12% (and ≥200 mL), 15 min after salbutamol† 200 to 400 µg, and an asthma symptom score of at least 2 on at least 4 of the last 7 evaluable days of the run-in period		Secondary: Lung function, asthma symptoms, use of rescue medications, adverse events	between treatment groups. The adjusted mean rates of moderate/severe exacerbations per year calculated at weeks one to 24, one to eight, and nine to 16 were similar between treatment groups (P=NS). The adjusted mean rate of moderate/severe exacerbations per year calculated at weeks 17 to 24 of fluticasone propionate -salmeterol was lower than budesonide-formoterol (P=0.006). Secondary: There were no statistically significant differences in morning and evening PEF, asthma symptoms, symptom-free days, symptom-free nights, rescue medication usage, asthma control, and incidence and types of adverse events observed between treatment groups.
Lötvall et al.[163] (2006) <u>Study A</u> Fluticasone propionate - salmeterol 100-50 µg as a single dose vs budesonide-formoterol 160-4.5 µg as a single dose vs placebo <u>Study B</u> Fluticasone propionate -	Study A: DB, PC, RT, SC, 3-way XO Study B: DB, MC, RT, XO Patients ≥18 years of age with asthma for ≥6 months, pre bronchodilator FEV_1 of >50% predicted of normal, FEV_1 ≥15% of predicted value 15 min after receiving 400 µg salbutamol; in Study A, patients were receiving budesonide 400 to 1,200 µg (or equivalent) at least	<u>Study A</u> N=33 3 weeks <u>Study B</u> N=75 12 weeks	<u>Study A</u> Primary: Mean change from predose FEV_1 to 16 hours postdose Secondary: Mean change in FEV_1 from predose over 24 hours postdose <u>Study B</u> Primary: Slope of decline in FEV_1 from two hours postdose, area under FEV_1 curve, mean change from predose FEV_1 at 12 hours postdose	<u>Study A:</u> Primary: Patients in both the fluticasone propionate -salmeterol and budesonide-formoterol groups had statistically significant greater FEV_1 values at 16 hours postdose in comparison to those in the placebo group (-0.5 L difference; P<0.001). There was no statistically significant difference in FEV_1 values at 16 hours postdose between the active treatment groups (P=0.617). Secondary: Patients in both the fluticasone propionate -salmeterol and budesonide-formoterol groups had a statistically significant mean change in FEV_1 at each scheduled evaluation compared to those in the placebo group. There was no statistically significant difference in mean change of FEV_1 between the active treatment groups. <u>Study B:</u> There were no statistically significant differences between the fluticasone propionate -salmeterol and budesonide-formoterol groups in regards to all primary endpoints.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 100-50 µg, 1 inhalation BID vs budesonide-formoterol 160-4.5 µg, 1 inhalation BID	4 weeks prior to study; in Study B, patients were receiving budesonide or beclomethasone 800 to 1,200 µg/day or fluticasone propionate 400 to 600 µg/day for at least 4 weeks prior to study		Secondary: Serial FEV_1 measurements following single dose after 4 weeks treatment	Secondary: There was no statistically significant difference in mean FEV_1 from baseline or FEV_1 from predose over 24 hours after four weeks treatment between the active treatment groups.
O'Connor et al.[164] (2010) Month 1: Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via PMDI vs fluticasone propionate - salmeterol 250-50 µg, 1 inhalation BID via DPI Months 2 to 7: Patients receiving fluticasone propionate - salmeterol continued therapy (FD), whereas those who received	OL, Phase III, RCT Patients ≥12 years of age with moderate to severe asthma	N=1,225 7 months	Primary: AQLQ, ACQ, ATSM and OEQ Secondary: Not reported	Primary: For AQLQ, no differences were observed between treatment groups in the percentages of patients with clinical meaningful improvements (≥0.5) in overall score. Although improvements were statistically significantly greater (P≤0.04) in the majority of domains for AMD vs either FD regimens, no clinically meaningful between group differences were noted. There were no statistically significant differences between FD regimens in mean improvement from baseline for overall or individual domain scores at the end of treatment. At the end of treatment, the mean change from baseline for all treatment groups exceeded the minimum important difference (0.5) for the ACQ, with no statistically significant or clinically meaningful between group changes noted (P values not reported). As indicated by the ATSM overall score at the end of treatment, patients reported significantly greater treatment satisfactions with AMD vs FD fluticasone propionate -salmeterol (P=0.020); there was no significant between group differences between the budesonide-formoterol FD and fluticasone propionate -salmeterol FD groups. Patients in both budesonide-formoterol groups reported significantly greater treatment satisfaction than those in the fluticasone propionate -salmeterol group for the attributes of timely relief of symptoms (P≤0.037) and feel medication working (P≤0.020). Patients in the budesonide-formoterol AMD group reported significantly greater treatment satisfaction for the attribute of dosing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
budesonide-formoterol were randomized to continue budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD) OR to budesonide-formoterol 160-4.5, 2 inhalations QD or 4 inhalations BID (AMD). All patients received their usual asthma therapy for 10 to 14 days prior to randomization.				management than patients in the fluticasone propionate -salmeterol FD group (P<0.001), and reported significantly greater treatment satisfaction of the attributes of daily activity, leisure activity and dosing management than patients in the budesonide-formoterol group FD (P≤0.048). For the predefined item "During the past week, you could feel your study medication begin to work right away", 71, 71 and 59% of patients in the budesonide-formoterol AMD, budesonide/formoterol FD and fluticasone propionate -salmeterol FD groups responded positively at the end of treatment. The differences observed between the budesonide-formoterol groups and the fluticasone propionate -salmeterol groups were statistically significant (P≤0.002). For the predefined item "During the past week, you were satisfied with how quickly you felt your study medication begin to work", 78, 80 and 73% of patients in the budesonide-formoterol AMD, budesonide-formoterol FD and fluticasone propionate -salmeterol FD groups responded positively at the end of treatment. The difference between the FD budesonide-formoterol and fluticasone propionate -salmeterol groups was small but statistically significant (P=0.025). Secondary: Not reported
Busse et al.[165] (2008) <u>Treatment period I:</u> Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID via Diskus vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD)	MC, OL, RCT, Patients ≥12 years of age with an asthma diagnosis for ≥6 months and who are in stable condition, required to have a pre bronchodilator FEV_1 ≥50% of predicted normal and to have been maintained on a daily medium dose ICS or ICS/LABA	N=1,225 Treatment Period I: 1 month Treatment Period II: 6 months	Primary: Number of exacerbations/patient-treatment year, percentage of patients with ≥1 exacerbations, and time from first dose to first exacerbation Secondary: Predose FEV_1, morning PEF, morning and evening asthma	Primary: There was no significant difference seen in the treatment groups and the time to first exacerbation (P value not reported). There was no significant difference seen in the treatment groups and the percentage of patients with at least one exacerbation, for the AMD budesonide-formoterol group the percentage was 8.0, 8.8% in the FD budesonide-formoterol group and 9.2% in the fluticasone propionate -salmeterol group (P value not reported). There was no significant difference seen in the treatment groups and the total number of exacerbations/patient treatment year, for the AMD budesonide-formoterol group the value was 0.196, 0.240 in the FD budesonide-formoterol group and 0.189 in the fluticasone propionate -salmeterol group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment period II: Fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID via Diskus vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI (FD) vs budesonide-formoterol 160-4.5 µg AMD (adjustable from 2 inhalations BID to 2 inhalations QD or 4 inhalations BID all via Diskus)	for ≥12 weeks before screening		symptom scores, nighttime awakenings, daily rescue medication use, average daily symptom scores, symptom-free days, rescue medication-free days, and safety	Secondary: No statistically significant differences were seen in predose FEV_1, for the AMD budesonide-formoterol group the change was 0.13 L, 0.15 L in the FD budesonide-formoterol group and 0.16 L in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in morning PEF, for the AMD budesonide-formoterol group the change was 34.73 L/minute, 30.86 L/minute in the FD budesonide-formoterol group and 33.59 L/minute in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in morning and evening asthma symptom scores, for the AMD budesonide-formoterol group the change was -0.39, for the FD budesonide-formoterol group the score was -0.37 and -0.35 L in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in nighttime awakenings. For the adjustable dose budesonide-formoterol group the percent change was 10.03%, 10.02% in the FD budesonide-formoterol group and 7.73% in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in the percentage of symptom-free days, for the AMD budesonide-formoterol group the percent change was 26.59%, 25.80% in the FD budesonide-formoterol group and 25.39% in the fluticasone propionate -salmeterol group (P value not reported). No statistically significant differences were seen in the percentage of rescue medication-free days, for the AMD budesonide-formoterol group the percent change was 41.84%, 41.24% in the FD budesonide-formoterol group and 38.85% in the fluticasone propionate -salmeterol group (P value not reported). All treatment groups were well tolerated. Adverse events were in general mild (56.1%) or moderate (38.4%), and no study medication adverse events were considered serious.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kuna et al.[166] (2007) Budesonide-formoterol 160-/4.5 µg, 1 inhalation BID, and additional inhalations as needed vs budesonide-formoterol 320-9 µg, 1 inhalation BID and terbutaline as needed vs fluticasone propionate - salmeterol 125-25 µg, 2 inhalations BID and terbutaline as needed Both FD treatment groups also had terbutaline as an as needed reliever medication.	DB, DD, PG, RCT Patients ≥12 years of age with an asthma diagnosis ≥6 months, using an ICS ≥3 months, FEV_1 ≥50% predicted normal, and ≥12% reversibility following terbutaline and ≥1 asthma exacerbation in previous 1 to 12 months	N=3,335 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit or the need for oral steroids ≥3 days) Secondary: Exacerbation rates, total number of severe exacerbations, number of patients having ≥1 hospitalization, number of mild exacerbation days, asthma symptom total score, morning and evening PEF, FEV_1, asthma symptom score, asthma induced night-awakenings, symptom-free days, as-needed medication free days, asthma-control days, number of mild exacerbations	Primary: The budesonide-formoterol 160-4.5 µg group prolonged the time to first severe exacerbation when compared to the fluticasone propionate - salmeterol (P=0.0034) and budesonide-formoterol 320-9 µg groups (P=0.023). There was a 33% reduction in the HR for a first severe exacerbation with the budesonide-formoterol 160-4.5 µg group compared to the fluticasone propionate -salmeterol group (P=0.003), and a 26% reduction when compared to the budesonide-formoterol 320-9 µg group (P=0.026). Secondary: Exacerbation rates were 19, 16 and 12 events/100 patients/six months for the fluticasone propionate -salmeterol group, the budesonide-formoterol 320-9 µg group and the budesonide-formoterol 160-4.5 µg group. The difference between the budesonide-formoterol 160-4.5 µg group, the fluticasone propionate -salmeterol group (P<0.001) and the budesonide-formoterol 320-9 µg group (P=0.0048) were statistically significant. However the difference between the fluticasone propionate -salmeterol group and the budesonide-formoterol 320-9 µg group was not statistically significant (P=0.1). The total number of severe exacerbations were 208, 173, and 125 in the fluticasone propionate -salmeterol, budesonide-formoterol 320-9 µg and budesonide-formoterol 160-4.5 µg groups, respectively (P value not reported). The percentage of patients having at least one hospitalizations/emergency room visit was 6, 5 and 4% in the fluticasone propionate -salmeterol, budesonide-formoterol 320-9 µg and budesonide-formoterol 160-4.5 µg groups, respectively. The difference was significant between the budesonide-formoterol 160-4.5 µg group and the fluticasone propionate - salmeterol group (P=0.047), but not between the two budesonide-formoterol groups or between the budesonide-formoterol 320-9 µg and fluticasone propionate -salmeterol groups (P=0.066). There were no significant differences seen between the three treatment groups in the number of mild exacerbation days. Overall 59, 63 and 61%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(defined as a day with any of one the following: morning PEF ≥20% below baseline, daily as-needed medication use ≥2 inhalations or a night with asthma-related awakenings), and safety	in the fluticasone propionate -salmeterol group, the budesonide-formoterol 320-9 µg group and the budesonide-formoterol 160-4.5 µg group experienced a mild exacerbation (P value not reported). There were no significant differences between all three treatment groups in asthma symptom total score (1.03,1.07 and1.06), percentage of symptom-free days (46.0, 44.6 and 44.2%), percentage of asthma-control days (43.7, 42.2 and 41.3%), percentage of night-time awakenings (14.0,14.6 and 14.1%), total number of inhalations/day (0.96,1.05 and 1.02) for the fluticasone propionate -salmeterol, the budesonide-formoterol 320-9 µg and the budesonide-formoterol 160-4.5 µg groups, respectively (P values not reported). There were no significant differences found between all three treatment groups in FEV_1 (2.67, 2.66 and 2.69 L), morning PEF (367, 362 and 363 L/minute), evening PEF (370, 366 and 368 L/minute) for the fluticasone propionate -salmeterol, the budesonide-formoterol 320-9 µg and the budesonide-formoterol 160-4.5 µg groups, respectively (P values not reported). All three treatment groups reported no significant differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and nasopharyngitis.
Palmqvist et al.[167] (2001) Budesonide-formoterol 160-4.5 µg, 1 inhalation as a single dose vs budesonide-formoterol 160-4.5 µg, 2 inhalations as	DB, PC, RCT, XO Adult asthmatic patients (mean predicted FEV_1 of 78%, mean reversibility of 19%)	N=30 4 days	Primary: Mean FEV_1 at 15 minutes after inhalation Secondary: Time to bronchodilation (defined as >15% increase in FEV_1 from baseline), absolute FEV_1 at three minutes, and	Primary: Both budesonide-formoterol doses demonstrated improvements in FEV_1 compared to fluticasone propionate -salmeterol and placebo at 15 minutes postdose (P<0.001). Secondary: At one hour, bronchodilation was achieved in 47% of patients in the fluticasone propionate -salmeterol group, 73% of those in the budesonide-formoterol one inhalation group and 77% of those in the budesonide-formoterol two inhalations group. Both doses of budesonide-formoterol also demonstrated significant improvements in FEV_1 at three minutes (P<0.001) and at 60 minutes (P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
a single dose vs fluticasone propionate -salmeterol 250-/50 µg, 1 inhalation as a single dose vs placebo			FEV_1 at time points ≤60 minutes	values not reported) compared to fluticasone propionate -salmeterol and placebo.
Aalbers et al.[168] (2004) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID (AMD) vs budesonide-formoterol 160-4.5 µg, 2 inhalations BID (FD) vs fluticasone propionate -salmeterol 250-50 µg, 1 inhalation BID (FD) During a 4 week	DB (4 weeks), ES (6 months), OL Patients with moderate-severe asthma, mean symptom score 1.5, mean FEV_1 84% predicted, mean ICS dose 735 µg/day	N=658 4 week DB period plus a 6 month OL extension	Primary: Odds of achieving a WCAW Secondary: Exacerbation rate and use of reliever medication	Primary: There was no difference in the OR pertaining to WCAW observed in the FD treatment groups (P value not reported). There was a significant increase in the odds of achieving WCAW observed in the budesonide-formoterol AMD group in comparison to the budesonide-formoterol FD group during the open period, regardless of a 15% decrease in the average use of study drug (OR, 1.335; 95% CI, 1.001 to 1.783; P=0.049). Secondary: Patients in the budesonide-formoterol AMD group had a significantly lower exacerbation rate (40%) compared to those in the fluticasone propionate -salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (P=0.018 and P value not significant, respectively). Patients in the budesonide-formoterol AMD group used significantly less reliever medication during the open study period vs those in the budesonide-formoterol and the fluticasone propionate -salmeterol FD groups (P=0.001 and P=0.011, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DB period, the budesonide-formoterol AMD and FD groups received 2 inhalations BID, and those in the fluticasone propionate - salmeterol group received 1 inhalation BID. During a 6 month extension period, all FD groups remained the same and the budesonide-formoterol AMD group could decrease dose to 1 inhalation BID, or increase dose up to 4 inhalations BID for 7 to 14 days based on asthma symptoms.				
Edwards et al.[169] (2007) Budesonide vs budesonide-formoterol (FD)	MA Patients with moderate to severe asthma	15 trials 12 to 52 weeks	Primary: Treatment failure Secondary: Hospitalizations, emergency visits, use of oral steroids	Primary: Patients in the budesonide-formoterol group demonstrated 50% less treatment failure in comparison to those who received budesonide treatment alone (RR, 1.50; 95% CI, 1.12 to 2.02; P=0.007). Although there seemed to be a favorable trend in the reduction of treatment failure observed in the budesonide-formoterol (AMD) group vs the budesonide-formoterol FD group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol (AMD) vs fluticasone propionate - salmeterol (FD)				There was no significant difference observed between those in the budesonide-formoterol group and those in the fluticasone propionate - salmeterol group in regards to treatment failure (P=0.86). Secondary: Patients in the fluticasone propionate -salmeterol group had a 49% greater risk of hospitalizations/accident and emergency visits compared to those in the FD budesonide-formoterol group (RR, 1.49; 95% CI, 1.07 to 2.08; P=0.02). Patients in the budesonide-formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits vs those treated with FD budesonide-formoterol (RR, 0.72; 95% CI, 0.52 to 0.99; P=0.04). Budesonide alone, was associated with a greater risk (51%) in the use of oral steroids in comparison to budesonide-formoterol (RR, 1.51; 95% CI, 1.10 to 2.09; P=0.01). Patients in the budesonide-formoterol-AMD group had a lower requirement for oral steroids than those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; P=0.01). Patients in the budesonide-formoterol-AMD treatment group experienced a 19% decreased risk in use of oral steroids vs those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; P=0.01).
Cates et al.[170] (2013) Budesonide-formoterol vs ICS plus reliever therapy vs	MA (13 RCTs) Adults and children with chronic asthma	N=13,152 At least 12 weeks	Primary: Exacerbations requiring hospitalization, exacerbations requiring oral corticosteroids, serious adverse events (including mortality and life-threatening events) and growth (in	Primary: Exacerbations of asthma causing hospital admissions Twenty one adults and adolescents treated with budesonide-formoterol 160-4.5 µg experienced an exacerbation leading to hospitalization compared to 26 patients treated with current best practice (Peto OR, 0.81; 95% CI, 0.45 to 1.44). Compared to ICS with a separate reliever medication, there was no statistically significant difference in exacerbations of asthma causing hospital admissions with budesonide-formoterol (Peto OR, 0.56; 95% CI, 0.28 to 1.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
current best practice			children) Secondary: Severe exacerbations (composite outcome of hospitalization/ emergency room visit/oral steroid course), morning and evening PEF, FEV_1, rescue medication use per day, symptoms/symptom-free days, nocturnal awakenings and quality of life	Significantly fewer children treated with budesonide-formoterol were hospitalized for asthma exacerbations compared to those treated with higher doses of ICS (OR, 0.33; 95% CI, 0.15 to 0.77). *Exacerbations of asthma treated with oral corticosteroids* There was a statistically significant reduction between treatment with budesonide-formoterol 160-4.5 µg and current best practice with regard to the risk of asthma exacerbation requiring treatment with oral corticosteroids (Peto OR, 0.83; 95% CI, 0.70 to 0.98). The NNT was 90. There was a significant reduction in the number of patients requiring a course of steroids with budesonide-formoterol compared to ICS plus a separate reliever medication (OR, 0.54; 95% CI, 0.45 to 0.64). The NNT was 14. *Serious adverse events* No significant differences were reported between budesonide-formoterol 160-4.5 µg and current best practice in the risk of fatal or non-fatal serious adverse events (fatal events: Peto OR, 1.95; 95% CI, 0.53 to 7.21; non-fatal events: OR, 1.20; 95% CI 0.90 to 1.60). The overall number of events was too small to rule out the possibility of a clinically important increase or decrease in serious adverse events. No significant difference was observed in either fatal (Peto OR, 0.37; 95% CI, 0.05 to 2.62) or non-fatal adverse events (OR, 0.97; 95% CI, 0.73 to 1.29) between budesonide-formoterol and ICS plus a separate reliever medication. Secondary: Severe exacerbations requiring medical intervention In seven studies, there was no significant reduction in the time to a severe exacerbation between patients treated with budesonide-formoterol 160-4.5 µg or current best practice (HR, 0.94; 95% CI, 0.85 to 1.04). There was a significant reduction in the time to a serious exacerbation with budesonide-formoterol compared to high dose ICS plus a separate reliever therapy (HR 0.59; 95% CI 0.49 to 0.70).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Change in morning PEF and FEV_1 Data were not available for this outcome for budesonide-formoterol 160-4.5 µg treatment compared to current best practice. There was a significant increase in PEF in the budesonide-formoterol group compared to treatment with a higher dose of budesonide (mean difference, 22.29 L/min; 95% CI, 17.62 to 26.95). There was an increase in FEV_1 with budesonide-formoterol compared to higher doses of budesonide (mean difference, 0.10 L; 95% CI, 0.07 to 0.13). There was no significant difference in PEF for FEV_1 between patients treated with budesonide-formoterol compared to higher doses of ICS. *Rescue medication use* One study evaluated rescue medication use and reported a difference of -0.16 puffs/day (95% CI, -0.27 to -0.05) with budesonide-formoterol 160-4.5 µg compared to current best practice. There was a reduction in rescue medication use in favor of budesonide-formoterol compared to higher doses of budesonide (mean difference, -0.37 puffs per day; 95% CI, -0.49 to -0.25). *Quality of life* On average, children treated with budesonide-formoterol experienced two fewer nocturnal awakenings per night compared to children treated with higher doses of ICS (95% CI, -3.33 to -0.67). *Annual height gain* The mean increase in height over one year in the budesonide-formoterol group was 5.3 cm (range 1 to 14 cm), significantly higher compared to 4.3 cm (range -2 to 15 cm) in the ICS treatment group.
Sears et al.[171] (2008)	MC, OL, PG, RCT Patients ≥12 with	N=1,538 6 months	Primary: Time to first severe asthma	Primary: No significant difference was found between the two treatment groups in time to first severe exacerbation (HR, 0.99; 95% CI, 0.70 to 1.41; P=0.95).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Budesonide-formoterol 160-4.5 µg, 1 inhalation BID and additional doses as needed vs conventional best practice therapy (could include any therapy including either ICS-LABA combination product, but not the use of budesonide-formoterol as both maintenance and reliever therapy)	asthma for a minimum of 3 months, use of ≥400 µg of ICS daily, treatment with ICS alone and a history of uncontrolled disease (≥3 inhalations of as needed rescue therapy during the last 7 days prior to enrollment) or daily maintenance treatment with an ICS and LABA		exacerbation Secondary: Number of severe asthma exacerbations, mean use of as needed medication, PEF, ACQ-5	Secondary: The mean number of exacerbations per patient per year was 0.19 for the budesonide-formoterol group compared to 0.21 for the convention treatment group (HR, 0.92; 95% CI, 0.67 to 1.28; P=0.63). Total days of oral corticosteroid use were 17% lower in the budesonide-formoterol group compared to the conventional group (590 vs 709 days). Mean as-needed reliever use decreased from 1.25 to 0.94 inhalations per day with budesonide-formoterol compared to a decrease from 1.22 to 1.09 inhalations per day in the conventional therapy (P=0.0036). There were a total of 15 patients in the budesonide-formoterol group who required >8 as needed inhalations on at least one day, compared to 30 subjects in the conventional treatment group (P=0.028). PEF increased from 94.8 to 98.0% predicted in the budesonide-formoterol group compared to an increase from 84.1 to 96.3% in the conventional group a difference that was not significant (P=0.46). The ACQ-5 score decreased from 1.27 to 1.08 in the budesonide-formoterol group compared to a decrease from 1.24 to 1.09 in the conventional treatment group, a difference that was not significant (P=0.46).
Louis et al.[172] (2009) Budesonide-formoterol 160-4.5 µg, 1 inhalation BID with additional inhalations as needed via MDI vs	MC, OL, PG, RCT Patients ≥12 years of age with an asthma diagnosis for >3 months and prescribed ICS at a dose of ≥500 µg/ day beclomethasone dipropionate equivalent with or without other controller therapies,	N=908 26 weeks	Primary: Time to first severe asthma exacerbation (defined as deterioration in asthma leading to hospitalization, emergency room visit, or equivalent) or oral steroid treatment for ≥3 days	Primary: There was no difference in the time to first severe asthma exacerbation for patients treated with budesonide-formoterol compared to CBP (P=0.75). Secondary: Only 2.7% of patients who received budesonide/formoterol and 4.1% of patients treated according to CBP experienced a severe asthma exacerbation during treatment. Twelve patients in the budesonide-formoterol group experienced a total of 14 exacerbations, and 19 patients in the CBP group experienced a total of 25 exacerbations (annual rate including all patients, 0.074 vs 0.13 per patient-year; P=0.09). A similar percentage of patients in both groups had ≥1 day during which at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
conventional best practice (CBP) treatment (multiple controller therapies allowed, ICS and ICS/LABAs at any dose and add-on oral leukotriene antagonist or xanthenes if warranted) The CBP group was treated in a stepwise approach in accordance with the Global Initiative for Asthma guidelines.	if a patient was using ICS monotherapy, they needed to use ≥3 inhalations of as-needed medication for symptom relief during the last 7 days before enrolment		Secondary: Number of severe asthma exacerbations, the mean use of as-needed medication (reliever medication) and prescribed asthma medications and scores on ACQ5, SATQ	least one dose of an as-needed medication was required (58.5 and 63.5% for budesonide-formoterol and CBP groups, respectively; P value not reported). The mean daily dose of inhaled steroid was significantly lower in the budesonide-formoterol group compared to the CBP group (482 vs 589 µg daily; P<0.0001). In the budesonide/formoterol group, the mean ACQ5 score assessing symptom control and activity limitation during the treatment period, decreased by -0.30 compared to -0.17 in the CBP group (P<0.01). Both groups showed similar overall treatment satisfaction (improvement in SATQ overall score) from enrolment to the end of the study (P value not reported).
Marceau et al.[173] (2006) Fluticasone propionate - salmeterol or budesonide-formoterol (fixed-dose inhaler) vs combination of ICS (fluticasone propionate, budesonide, or beclomethasone) and a LABA	RETRO Patients 16 to 44 years of age who had not been on combination or concurrent ICS and LABA therapy within the past year	N=5,118 1 year	Primary: Number of prescription renewals during the first year of treatment Secondary: The rate of moderate to severe asthma exacerbations (defined as a filled prescription of an ICS, an emergency department visits or hospitalization for asthma) during	Primary: An estimation of 44.2% of patients started on a combination therapy and 51.5% of patients started on concurrent therapy did not renew their prescription during the first year of treatment (P=0.0001). The number of prescriptions filled on average during the first year after treatment initiation was 3.5 for combination therapy and 2.7 for concurrent therapy (P value not reported). Secondary: Concurrent users had more exacerbations (1.1 vs, 0.7; P<0.0001) emergency department visits (0.4 vs 0.2; P<0.0001), hospitalizations (0.03 vs 0.01; P=0.78), and mean number of doses per week of short-acting inhaled β_2-agonists (7.0 vs 5.7; P<0.0001) compared to combination users.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(salmeterol or formoterol)			the first year of treatment, and weekly number of doses of short-acting inhaled β_2-agonists	
Scicchitano et al.[174] (2004) Budesonide-formoterol 160-4.5 µg, 2 inhalations QD with additional inhalations as needed vs budesonide 160 µg, 2 inhalations BID plus terbutaline 0.4 mg inhalations as needed	DB, PG, RCT Patients 11 to 80 years of age with symptomatic asthma, mean FEV_1 70% of predicted, mean ICS dose 746 µg/day	N=1,890 12 months	Primary: Time to first severe exacerbation (defined as hospital/emergency room visit, oral steroids or fall in morning PEF to <70% of baseline for two consecutive days) Secondary: Number of severe exacerbations, use of as needed medication, mean daily ICS dose, and number of asthma control days	Primary: Patients in the budesonide-formoterol group had prolonged time to first exacerbation, and a 39% lower risk of having a severe exacerbation compared to the budesonide group (P<0.001). Secondary: Patients in the budesonide-formoterol group had 45% fewer severe exacerbations resulting in medical interventions/patient compared to those in the budesonide group (P<0.001). Patients in the budesonide-formoterol group also had less utilization of as-needed medication (P<0.001), and a lower mean daily ICS dose (466 vs 640 µg/day, respectively) compared to those in the budesonide group. Overall, those in the budesonide-formoterol group experienced 31 more asthma control days and 12 more undisturbed nights/patient-year vs those in the budesonide group (P value not reported).
Rabe et al.[175] (2006) Budesonide-formoterol 80-4.5 µg, 2 inhalations QD in the evening with additional inhalations as needed	AC, DB, MC, PG, RCT Patients 11 to 79 years of age with an asthma diagnosis for ≥6 months, FEV_1 60 to 100% predicted normal, >12% reversibility of baseline FEV_1 15	N=697 6 months	Primary: Morning PEF Secondary: FEV_1, evening PEF, as needed inhalations, as needed medication-free days, asthma symptom score,	Primary: Patients in the budesonide-formoterol group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the six month treatment period (34.5 vs 9.5 L/minute, respectively; P<0.001). Secondary: Both treatment groups were associated with an increase in mean FEV_1, but those in the budesonide-formoterol group had statistically significant greater improvements compared to those receiving budesonide alone (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide 160 µg, 2 inhalations QD in the evening plus terbutaline 0.4 mg as needed	minutes after terbutaline 1 mg inhalation, all patients had received an ICS 200 to 500 µg/day for ≥3 months at a constant dose for ≥30 days prior to study and were required to have had ≥7 inhalations of as-needed medication during the last 10 days of the run-in period but <10 inhalations on any single day		nighttime awakenings, symptom free days, asthma control days, and risk of exacerbation	Patients in the budesonide-formoterol group also had greater improvements in evening PEF from baseline than those in the budesonide group. Patients in the budesonide-formoterol group had statistically significantly lower asthma symptom scores in comparison to those who were receiving budesonide (P<0.001). There was also a statistically significant improvement in both symptom free days and asthma control-days observed in the budesonide/formoterol group vs those in the budesonide group (P<0.01). Those in the budesonide-formoterol group had less utilization of as-needed medication, along with eight percent more as-needed medication-free days vs those in the budesonide group (P<0.001). Patients in the budesonide-formoterol had a 54% lower risk in having an exacerbation in comparison to those in the budesonide group (P=0.0011), as well as 90% fewer hospitalizations/emergency department treatments vs those in the budesonide group (P=0.026).
Maspero et al.[176] (2008) Fluticasone propionate - salmeterol 100-50 µg, 1 inhalation BID vs montelukast 5 mg QD	AC, DB, RCT Patients 6 to 14 years of age with asthma for at least 6 months	N=548 12 weeks	Primary: Change from baseline in morning PEF Secondary: Tolerability was assessed by recording adverse events and asthma exacerbations	Primary: The mean changes from baseline in morning PEF was 45.8±2.82 L/min with salmeterol-fluticasone propionate and 28.7±2.86 L/min with montelukast (treatment difference, 17.16 L/min; P<0.001). Secondary: Both treatments were well tolerated with a similar number of patients reporting adverse events (155/281 [55%] in the salmeterol-fluticasone propionate group; 153/267 [57%] in the montelukast group). The mean exacerbation rates over 12 weeks were 0.12 in the salmeterol-fluticasone propionate group and 0.30 in the montelukast group (P<0.001).
Sorkness et al.[177] (2007) Fluticasone	DB, PG, RCT Patients 6 to 14 years of age with	N=285 48 weeks	Primary: Percent of asthma control days; use of oral	Primary Percent of asthma control days averaged 64.2% for fluticasone propionate monotherapy, 59.6% for PACT combination, and 52.5% for montelukast monotherapy. The fluticasone propionate monotherapy group gained an

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propionate - salmeterol 100-50 µg QAM and salmeterol 50 µg QPM (PACT combination) vs fluticasone propionate 100 µg BID (fluticasone propionate monotherapy) vs montelukast 5 mg QPM (montelukast monotherapy)	mild to moderate asthma, >4 hour post-bronchodilator FEV_1 ≥80% of predicted normal and ≥70% at randomization plus methacholine FEV_1 ≤12.5 mg/ml		corticosteroids; use of non-study asthma medications; daytime symptoms; nighttime awakenings; unscheduled health care visits; emergency department visits, or hospitalizations for asthma; and school absenteeism for asthma. Secondary: Percent of episode-free days; number of exacerbations requiring prednisone; time to first exacerbation requiring prednisone; time to treatment failure; Asthma Control Questionnaire; pulmonary function and growth	average of 42 asthma control days per year compared with the montelukast monotherapy group (P=0.004). The change in asthma control days from baseline to end of treatment was significantly greater for fluticasone propionate monotherapy vs montelukast, and PACT combination vs montelukast, but not for fluticasone propionate monotherapy vs PACT combination. During the 48 weeks, the percentages of patients who achieved 20% more asthma control days during the treatment period compared with the run-in period were 65% for fluticasone propionate monotherapy, 66% for PACT combination, and 50% for montelukast. The NNT for both fluticasone propionate monotherapy and PACT combination compared with montelukast was approximately 6.5, meaning that seven patients would need to be treated with fluticasone propionate monotherapy or PACT combination instead of montelukast to achieve 1 additional treatment response defined as a 20% increase in asthma control days. Secondary: Compared with montelukast monotherapy, both fluticasone propionate monotherapy and PACT combination led to a greater percentage of episode-free days. Significant superiority of fluticasone propionate vs montelukast monotherapy (in favor of the former) for time to first prednisone burst (P=0.002) and time to treatment failure (P=0.015) but no differences for PACT combination vs montelukast. Twenty-eight treatment failures occurred, five with fluticasone propionate, eight with PACT combination, and 15 with montelukast, with the comparison for fluticasone propionate vs montelukast monotherapy significant (P=0.04). No significant difference between fluticasone propionate monotherapy vs PACT combination, or PACT combination vs montelukast in regard to ACQ score improvement, there was a significant difference with fluticasone propionate compared with montelukast (P=0.018). Pre bronchodilator FEV_1 (percent predicted) and FEV_1/FVC (percent) increased more with fluticasone propionate monotherapy than montelukast

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.001 for both measures) and PACT combination (P=0.01 for FEV_1). Treatment with montelukast did not improve these lung function measures. The mean change in FEV_1 percent predicted from baseline was 6.32% with fluticasone propionate monotherapy and 3.62% with PACT combination (P=0.06 for difference). For FEV_1/FVC, the mean change from baseline was 3.95% for fluticasone propionate monotherapy, compared with 1.76% for PACT combination (P=0.015 for difference). Change in bronchodilator response at 36 weeks compared with baseline was a mean decrease of 3.6% with fluticasone propionate monotherapy, compared with a 0.3% increase with PACT combination and a 1.69% increase with montelukast (P<0.001, fluticasone propionate vs montelukast). For the participant-measured outcome of percent predicted pre bronchodilator AM and PM PEFs, fluticasone propionate monotherapy and PACT combination resulted in comparable increases in mean change from baseline (5.1 and 5.4%, respectively, for AM recordings, and 2.9 and 4.3%, respectively, for PM recordings). Montelukast treatment did not significantly improve PEFs. Both fluticasone propionate and PACT combination were significantly superior to montelukast for change from baseline in both PEF measurements. Mean increase in height from baseline over 48 weeks was 5.3±1.8 cm with fluticasone propionate monotherapy, 5.3±1.5 cm with PACT combination, and 5.7±2.0 cm with montelukast monotherapy). Differences among the therapies in this outcome were about 0.4 to 0.46 cm less for fluticasone propionate monotherapy and PACT combination compared with montelukast monotherapy respectively, but of no statistical significance.
Peters et al.[178] (2007) LOCSS Fluticasone propionate -	DB, MC, RCT Patients ≥6 years of age with asthma, FEV_1 ≥60% of predicted value pre-bronchodilator,	N=500 16 weeks	Primary: Time to treatment failure Secondary: Measures of pulmonary	Primary: The rates of treatment failure were 20.2% in the fluticasone propionate group, 20.4% in the fluticasone propionate -salmeterol group, and 30.3% in the montelukast group (HR, 1.6; 95% CI, 1.1 to 2.6; P=0.03 for both comparisons). Secondary:

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salmeterol 100-50 µg QHS vs fluticasone propionate 100 µg BID vs montelukast 5 to 10 mg QD	reversibility of airway obstruction by ≥12% with the use of a β-agonist or provocative concentration of methacholine producing a 20% decrease in FEV_1 of ≤8 mg/mL within the previous 2 years; patients were stable on fluticasone 100 µg BID and step-down therapy was being attempted		function, measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients	Mean pre bronchodilator FEV_1 values were higher in the fluticasone propionate group (91.1% of the predicted value) and the fluticasone propionate -salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value; P=0.002 and P<0.001, respectively). Asthma control, as measured with the use of the Asthma Control Questionnaire, was better in the fluticasone propionate group and in the fluticasone propionate -salmeterol group than in the montelukast group. The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone propionate -salmeterol group (22.9 vs 17.1%; P=0.06) and in the fluticasone propionate group (22.9 vs 18.2%; P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone propionate group than in the montelukast group (16.7 vs 25.4%; P=0.04), with a similar trend in the fluticasone propionate -salmeterol group (17.3, vs 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6 to 85.8%.
Covar et al.[179] (2008) Fluticasone propionate -salmeterol 100-50 µg QAM and salmeterol 50 µg QPM vs fluticasone propionate 100 µg BID	DB, PC, PG, RCT Children 6 to 14 years of age with documented mild-moderate persistent asthma	N=285 48 weeks	Primary: Regression modeling was used to look for factors predictive of exacerbation Secondary: Not reported	Primary: Treatment with montelukast vs fluticasone propionate monotherapy (OR, 2.00; P=0.005) was a positive predictor for exacerbations. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs montelukast 5mg QD				
Ringdal et al.[180] (2003) Fluticasone propionate - salmeterol 100-50 µg BID plus oral placebo vs fluticasone propionate 100 µg BID and montelukast 10 mg QD	DB, DD, MC, PG RCT Patients 14 to 79 years of age with a diagnosis of asthma, history of receiving ICSs for ≥4 weeks prior to randomization, reversible airway obstruction, ≥15% increase in FEV_1 after β_2-agonist use, mean morning PEF 50 to 85% predicted, cumulative symptom score ≥8 during last 7 days of run-in period and symptoms on ≥4 of last 7 days of run-in	N=806 14 weeks	Primary: Mean morning PEF value Secondary: Evening PEF values, β_2-agonist use, daytime and nighttime symptom scores, changes in asthma medications, FEV_1, incidence and severity of asthma exacerbations, patient assessment of satisfaction with treatment, and physician assessment of effectiveness of treatment	Primary: Statistically significant improvement in morning PEF values in the fluticasone propionate -salmeterol group compared to the fluticasone propionate plus montelukast group (361 vs 191 L/minute; P<0.05). Secondary: Statistically significant improvement in FEV_1 values in the fluticasone propionate - salmeterol group compared to the fluticasone propionate plus montelukast group (mean treatment difference, 0.11 L; P<0.05). The fluticasone propionate -salmeterol group was significantly more likely to have a symptom-free day compared to the fluticasone propionate plus montelukast group (OR, 1.32; 95% CI, 1.05 to 1.65; P<0.05). The fluticasone propionate -salmeterol group was significantly more likely to have a rescue free day compared to the fluticasone propionate plus montelukast group (OR, 1.29; 95% CI, 1.02 to 1.63; P=0.03), but rescue-free nights did not reach statistical significance. A significantly lower number of patients in the fluticasone propionate - salmeterol group had an asthma exacerbation compared to patients in the fluticasone propionate plus montelukast group (9.6 vs 14.6%; P<0.05), but no significant difference between the groups in percentage of patients having moderate or severe asthma exacerbation (P=0.07) was noted. The time to first exacerbation was longer in the fluticasone propionate - salmeterol group compared to the fluticasone propionate plus montelukast group (P<0.05). Patient and physician satisfaction and assessment of treatment was higher in the fluticasone propionate -salmeterol group compared to the fluticasone propionate plus montelukast group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lemanske et al.[181] (2010) Fluticasone propionate 250 µg, BID (ICS step up therapy) vs fluticasone propionate - salmeterol 100-50 µg, BID (LABA step up therapy) vs fluticasone propionate 100 µg BID plus montelukast 5 or 10 mg/day (LTRA step up therapy) All patients received fluticasone propionate 100 µg BID during a 2 to 8 week run-in period. A treatment period was ranked as better than another if the total amount	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma diagnosed by a physician, the ability to perform reproducible spirometry, an FEV_1 ≥60% before bronchodilation, an increase in the FEV_1 ≥12% (bronchodilator reversibility) or a methacholine provocation concentration causing a 20% fall in the FEV_1 of ≤12.5 mg/mL	N=182 48 weeks	Primary: Differential response to each of the three step up therapies on the basis of fixed threshold criteria for the following three asthma-control measures: the need for treatment with oral prednisone for acute exacerbations, the number of asthma control days and FEV_1 Secondary: Not reported	Primary: Differential response to the three step up therapies A differential response occurred in 161/165 (98%) patients. The percentage of asthma control days differed according to season in all study groups, ranging from 71 to 79% in the winter and summer months. Asthma exacerbations were most frequent during winter months. The average FEV_1 varied by less than one percent across seasons. In pairwise comparisons, the proportion of patients who had a better response to LABA step up therapy was higher than the proportion with a better response to LTRA step up therapy (52 vs 34%; P=0.02), and the proportion with a better response to LABA step up therapy was higher than the proportion of with a better response to ICS step up therapy (54 vs 32%; P=0.004), whereas the response to LTRA and ICS step up therapies were similar. The primary outcome of the trial, a three-way comparison of step-up therapy with the use of rank-ordered logistic regression, predicted that the response to LABA step up was significantly more likely to be the best response, as compared to the response to LTRA step up (relative probability, 1.6; 95% CI, 1.1 to 2.3; P=0.004) and the response to ICS step up therapy (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of prednisone received during treatment was ≤180 mg, if the number of annualized asthma control days during the final 12 weeks of the period was increased by ≥31 days or if the FEV_1 at the end of the period was ≥5% higher. If the prednisone threshold was met, the number of asthma control days and FEV_1 were ignored. If the threshold for asthma control days was met, the FEV_1 was ignored. Otherwise the order of response was determined by the FEV_1.				
Nguyen et al.[182] (2005) Fluticasone propionate -	DB, RCT Pediatric patients 4 to 17 years of age with asthma, parent	N=39 12 months	Primary: Reducing the number of emergency department visits	Primary: Statistically significant decrease in the number of emergency department visit/year in the study group compared to the control group (1.2 to 0.8; P=0.017).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
salmeterol 100-50 to 250-50 µg BID vs usual care (all patients received ICS at some point during the study)	reported emergency room visits ≥5 in the past 2 years or 2 to 3 in the past 2 months, enrolled in Medicaid in Tennessee, Mississippi or Arkansas		and hospitalizations in minority inner-city children Secondary: Not reported	The risk of experiencing at least one hospitalization was reduced by 43% in the treatment group compared to the placebo group (risk ratio, 0.57; 95% CI, 0.19 to 1.71; P=0.31). The risk of experiencing an asthma exacerbation was reduced by 23% in the treatment group compared to the placebo group (P=0.09). Secondary: Not reported
Chronic Obstructive Pulmonary Disease				
Weir et al.[183](1999) Beclomethasone 750 to 1,000 µg BID vs placebo	DB, PC, PG, RCT Patients with COPD	N=98 24 months	Primary: Change in FEV_1, number of exacerbations Secondary: Change in histamine reactivity, respiratory symptoms	Primary: Decline in FEV_1 was less in the beclomethasone treated group although the difference did not reach statistical significance (mean FEV_1 decline: placebo 45.2 mL/year, budesonide 12.1 mL/year; [95% CI; -80 to 8 mL/year]). The actively treated group had fewer exacerbations per year although the difference was not statistically significant (mean exacerbation rates per year: placebo 0.57, budesonide 0.36). Secondary: Bronchial reactivity to inhaled histamine showed no significant change in either active or placebo groups (placebo -0.09, budesonide -0.13). There was no significant effect of active treatment on the Mahler dyspnea index over the study period (placebo 5.4, beclomethasone 6.7, P values not reported).
Bourbeau et al.[184] (1998) Budesonide 400 µg BID vs placebo	DB, PC, PG, RCT Patients with COPD 40 years of age or older who did not respond to oral corticosteroids	N=79 6 months	Primary: Decline in FEV_1 Secondary: Exercise capacity, dyspnea with exertion, quality of life, PEFR, respiratory	Primary: There was no difference in the change in FEV_1 from baseline between the treatment and placebo groups (-4 units difference; -95 to 87). Secondary: None of the secondary endpoints differed significantly between the two groups: (treatment difference, budesonide vs placebo). Exercise capacity as measured by the 6-minute walking test: (-28 units

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			symptom scores	difference, -45 to -10). Dyspnea with exertion: (0.1 units difference, -1.0 to 1.1) Quality of life: (1.3 units difference, -4.1 to 1.5) Morning PEFR increased more from baseline in the budesonide group than in the placebo group, but this was observed after only four weeks of treatment and the difference was no longer apparent after one month of treatment. Symptom scores with budesonide did not produce a significant improvement compared with placebo.
Pauwels et al.[185] (1999) Budesonide 400 µg BID vs placebo	DB, MC, PC, PG, RCT Current smokers 30 to 65 years of age with COPD	N=1,277 36 months	Primary: Change in FEV_1 over time Secondary: Adverse events	Primary: The median decline in FEV_1 over the three-year period was 140 mL in the budesonide group and 180 mL in the placebo group (P=0.05), or 4.3% and 5.3% of their respective predicted values (P=0.04). Secondary: More subjects in the budesonide group had skin bruising (10%) than the placebo group (4%) (P<0.001). Serious adverse events were equally distributed between the groups. Seventy patients were withdrawn from the study in the budesonide group as compared with 62 in the placebo group (P=0.51).
Vestbo et al.[186] (1999) Budesonide 800 µg QAM and 400 µg QPM for six months, followed by 400 µg BID for 30 months vs	DB, PC, PG, RCT Patients with COPD	N=290 36 months	Primary: Rate of FEV_1 decline Secondary: Decrease in symptoms	Primary: No significant effect of budesonide was found on the rate of FEV_1 decline. The crude rate of loss of lung function was 41.8 mL per year in the placebo group and 45.1 mL per year in the budesonide group. The difference in estimated rates of decline (3.1 mL per year [95% CI, -12.8 to 19.0]) was not significant (P=0.70). Secondary: In both treatment groups, symptoms decreased substantially during the study period but no differences between the two groups was observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				
Burge et al.[187] (2000) Fluticasone propionate 500 µg BID vs placebo	DB, PC, RCT Patients with COPD with a mean FEV_1 50% of predicted normal	N=751 36 months	Primary: Rate of decline in FEV_1 Secondary: Frequency of exacerbations, changes in health status, withdrawals due to respiratory disease, morning serum cortisol levels, adverse events	Primary: The annual rate of decline in FEV_1 was 59 mL per year in the placebo group and 50 mL per year in the fluticasone propionate group (P=0.16). The predicted mean FEV_1 at three and 36 months in the fluticasone group was 76 and 100 mL higher, respectively, than in the placebo group (P<0.001). Secondary: The median yearly exacerbation rate was lower in the fluticasone propionate group (0.99 per year) compared with the placebo group (1.32 per year), a reduction of 25% in those receiving fluticasone propionate (P=0.026). The respiratory health questionnaire score increased (i.e., health status declined) after the first six months of treatment and this increase was linear (P<0.001). The respiratory score worsened at a faster rate in the placebo group (3.2 units per year) than in the fluticasone propionate group (2.0 units per year) (P=0.004). More patients in the placebo group than in the fluticasone propionate group withdrew because of respiratory disease (25 vs 19%, respectively, P=0.034). There was a small decrease in mean cortisol concentrations with fluticasone propionate compared with placebo (P≤0.032). No decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects. Reported events were similar between treatments overall, with the exception of side effects secondary to inhaled glucocorticoids: hoarseness (35 vs 16), throat irritation (43 vs 27), and candidiasis of the mouth and throat (41 vs 24) were more common in the fluticasone propionate group than with placebo.
Paggiaro et al.[188] (1998)	DB, PC, RCT	N=281	Primary: Number of patients	Primary: More patients in the placebo group (37%) experienced at least one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate 500 µg BID vs placebo	Patients 50 to 75 years of age with COPD	6 months	who had at least one exacerbation at the end of the study period Secondary: Mean change from baseline in PEFR, daily symptom scores, frequency of adverse events	exacerbation than in the fluticasone propionate group (32%) (P<0.001). Secondary: The adjusted mean change from baseline daily PEFR in the placebo group was -2 L/min compared with 15 L/min in the fluticasone propionate group ([9-26], P<0.001). Symptom scores showed a distribution of significantly lower median daily cough scores in the fluticasone propionate group compared with the placebo group (P=0.004). The overall frequency of adverse events during treatment was similar in the two treatment groups, occurring in 68% of patients receiving placebo and 64% of patients receiving fluticasone propionate.
Vestbo et al.[189] (2016) Salford Lung Study Fluticasone furoate and vilanterol 100/25 µg inhaled QD via DPI vs usual care as determined by the prescriber	OL, MC, PG, PRO, RCT Patients ≥ 40 years of age with a diagnosis of COPD, ≥ 1 COPD exacerbation in the previous 3 years, and requiring maintenance inhaler therapy	N=2,799 1 year	Primary: The mean annual rate of moderate or severe exacerbations among patients with an exacerbation within 1 year before the trial Secondary: Rates of primary care or secondary care contact, rate of exacerbations among all trial patients, serious adverse events of pneumonia, and the frequency of other serious adverse events	Primary: The rate of moderate or severe exacerbations per year was 1.74 in the fluticasone furoate-vilanterol group, as compared to 1.90 in the usual care group. The rate of moderate or severe exacerbations was 8.4% lower (95% CI, 1.1 to 15.2; P=0.02) with fluticasone furoate/vilanterol therapy than with usual care. Secondary: There was no significant difference between treatment groups in the annual rate of COPD-related contacts to primary or secondary care. The rate was 1.7% (95% CI, −5.1 to 8.0) lower in the fluticasone furoate-vilanterol group than in the usual care group. There was no significant difference between treatment groups in the rate of first exacerbation in the time-to-event analysis when looking at the entire trial population (HR, 0.93; 95% CI, 0.85 to 1.02). A total of 7% of patients in the fluticasone furoate/vilanterol group and 6% of patients in the usual care group had one or more serious adverse event listed as pneumonia (IR, 1.1; 95% CI, 0.9 to 1.5). Serious adverse events occurred in 29% of patients in the fluticasone furoate-vilanterol group versus 27% of patients in the usual care group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Covelli et al.[190] (2015) Fluticasone furoate and vilanterol 100/25 µg inhaled QD via DPI vs tiotropium bromide 18 µg inhaled QD via DPI	AC, DB, DD, PG, RCT Patients ≥ 40 years of age with a diagnosis of COPD, ≥ 10 pack-year smoking history, FEV_1 30% to 70% of predicted, FEV_1 to FVC ratio ≤ 70%, and either CVD or a CVD risk factor other than smoking.	N=623 12 weeks	Primary: Change from baseline in 24-hour weighted mean FEV_1 on day 84 Secondary: Time to onset of bronchodilation, trough FEV_1, rescue medication use, SGRQ-C scores, CAT measures, CVD related measurements, and exacerbations	Primary: Both fluticasone furoate-vilanterol and tiotropium improved the 24-hour weighted mean FEV_1 from baseline after 12 weeks (LS mean change 117 mL and 95 mL respectively) with no significant difference between treatment groups (difference of 0.022 L; 95% CI, -0.012 to 0.055; P=0.201). Secondary: The median time to onset of bronchodilation was 17.0 minutes with fluticasone furoate-vilanterol compared to 20.5 minutes with tiotropium. The change from baseline in FEV_1 trough level did not differ significantly between treatment groups (difference of 0.005 L; 95% CI, -0.029 to 0.039). More subjects in the fluticasone furoate-vilanterol group than the tiotropium group demonstrated an onset of effect within the first 5 minutes of dosing (36% versus 23%, respectively). The percentage of rescue-free 24-hour periods was increased in the fluticasone furoate-vilanterol group compared with the tiotropium group during weeks 1 through 12 (LS mean change difference of 9.1%; 95% CI, 4.0 to 14.2). SGRQ-C scores and CAT measures improved from baseline in both treatment groups with no statically significant difference between groups. There was no clinically significant difference between treatment groups in the mean change from baseline for pulse rate, heart rate, or QTc intervals. Fewer patients in the fluticasone furoate-vilanterol group (2%) experienced a COPD exacerbation than in the tiotropium group (4%).
Vestbo et al.[191] (2016) SUMMIT Fluticasone furoate	AC, DB, MC, PC, PRO, RCT Patients 40 to 80 years of age with	N=16,485 33 months	Primary: All-cause mortality Secondary: On-treatment rate	Primary: Compared to placebo, all-cause mortality was unaffected by combination therapy with fluticasone furoate-vilanterol (HR, 0.88; 95% CI, 0.74 to 1.04; P=0.137) fluticasone furoate alone (HR, 0.91; 0.77 to 1.08; P=0.284) or vilanterol alone (HR, 0.96; 0.81 to 1.14; P=0.655).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and vilanterol 100/25 µg inhaled QD via DPI vs fluticasone furoate 100 µg inhaled QD via DPI vs vilanterol 25 µg inhaled QD via DPI vs placebo	FEV_1 between 50 to 70% of predicted, ratio of post-bronchodilator FEV_1 to FVC ≤0.70, ≥10 pack year smoking history, score of ≥2 on the modified Medical Research Council dyspnea scale, and a history of CVD or CVD risk.		of decline in FEV_1, a composite of CV events, exacerbations, and safety analyses	Secondary: The rate of decline in FEV_1 was reduced in the fluticasone furoate-vilanterol group (38 mL per year [SE 2.4]) compared to the placebo group (46 mL per year [SE 2.5]) with a between group treatment difference of 8 mL per year; 95% CI, 1 to 15). Similar findings were seen with the fluticasone furoate only group (difference of 8 mL per year; 95% CI, 1 to 14), but not with the vilanterol only group (difference of –2 mL per year; 95% CI, -8 to 5). Fluticasone furoate/vilanterol treatment had no effect on composite CV events compared to placebo (HR, 0.93; 95% CI, 0.75 to 1.14). Findings were similar for fluticasone furoate (HR, 0.90; 0.73 to 1.11) and vilanterol (HR, 0.99; 0.80 to 1.22). All treatments reduced the rate of moderate and severe exacerbations. Rates of pneumonia were similar between treatment group (5% in the placebo group, 6% in the fluticasone furoate-vilanterol group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) Rates of adverse CV events were also similar between treatment groups (17% in the placebo group, 18% in the fluticasone furoate-vilanterol group, 17% in the fluticasone furoate group, and 17% in the vilanterol group).
Martinez et al.[192] (2013) Fluticasone furoate-vilanterol 100-25 µg QD vs fluticasone furoate-vilanterol 200-25 µg QD vs	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70%	N=1,224 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary: CRQ-SAS, peak FEV_1, time to ≥100 mL improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV_1 over the first	Primary: The 100-25 µg and 200-25 µg combination regimens were associated with improvement in weighted mean postdose-FEV_1 compared to placebo (214 mL; 95% CI, 161 mL to 266 mL for the 100 µg dose comparison; and 209 mL; 95% CI, 157 mL to 261 mL for the 200 µg dose comparison, respectively) and fluticasone furoate monotherapy (168 mL; 95% CI, 116 mL to 220 mL for the 100 µg dose comparison; 168 mL; 95% CI, 117mL to 219 mL for the 200 µg dose comparison, respectively). In addition, the combination regimens were associated with an increase in trough FEV_1 compared to placebo (144 mL; 95% CI, 91 mL to 197 mL for the 100 µg dose comparison; and 131 mL; 95% CI, 80 mL to 183 mL for the 200 µg dose comparison, respectively). However, there was no significant difference between the combination regimen and vilanterol alone (45 mL; 95% CI, -8 mL to 97 mL for the 100 µg dose comparison; and 32 mL; 95% CI, -6 mL to 102 mL for the 200 µg dose comparison, respectively)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone furoate 200 µg QD vs fluticasone furoate 100 µg QD vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.	predicted and a score of ≥2 on the mMRC Dyspnea Scale		four hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	Secondary: From day one of the study postdose-FEV_1 and trough-FEV_1 were greater with fluticasone furoate-vilanterol and vilanterol compared to fluticasone furoate and placebo. Both parameters increased rapidly from day 1 to day 14 and were generally maintained thereafter. Over six months, scores on the dyspnea domain of the CRQ-SAS declined relative to placebo with both strengths of fluticasone furoate, but improved with both strengths of fluticasone furoate-vilanterol and with vilanterol alone. In the fluticasone furoate 100 µg and 200 µg arms adjusted mean peak FEV_1 was 24 mL (95% CI, -6 to 55) and 7 mL (95% CI, -23, to 37) respectively, greater than placebo while for vilanterol the adjusted mean increase from placebo was 147 mL (95% CI, 117 to 177). The equivalent values for fluticasone furoate-vilanterol 100-25 µg and 200-25 µg were 152 mL (95% CI, 122 to 182) and 141 ml (95% CI, 111 to 171), respectively. Other efficacy comparisons generally favored the use of fluticasone furoate-vilanterol compared to placebo. No increase was seen in on-treatment adverse events or serious adverse events, with active therapy vs. placebo. Exacerbations were infrequent but occurred more often in the placebo arm (21 events) than in any active treatment arm and more frequently in the vilanterol arm (18 events) than in the fluticasone furoate-containing arms (14 events).
Kerwin et al.[193] (2013) Fluticasone furoate-vilanterol 50-25 µg QD	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe	N=1,030 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary:	Primary: The 100-25 µg combination regimen was associated with improvement in weighted mean postdose-FEV_1 compared to placebo (173 mL; 95% CI, 123 to 224 mL) and fluticasone furoate monotherapy (120 mL; 95% CI, 70 to 170 mL). In addition, the combination regimen was associated with an increase in trough FEV_1 compared to placebo (115 mL; 95% CI, 60 mL to 169 mL). However, there was no significant difference between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone furoate vilanterol 100-25 µg QD vs fluticasone furoate 200 µg QD vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.	COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and a score of ≥2 on the mMRC Dyspnea Scale		CRQ-SAS, peak FEV_1, time to ≥100 ml improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV1 over the first four hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	combination regimen and vilanterol alone (48 mL; 95% CI, -6 to 102 mL). Similar results were observed with the 50 µg-25 µg compared to placebo. Secondary: For FEV_1 at other time points over 24 weeks, both strengths of fluticasone furoate-vilanterol showed rapid and sustained improvements over placebo, and were greater than the vilanterol monotherapy arm at all time points from day 14. Similarly, both combination strengths and vilanterol showed rapid and sustained effects on trough FEV_1 compared to placebo, and both combination strengths provided greater lung function effects than vilanterol at days 7, 28, 56, 84, 140 and 168, but only the 50 µg-25 µg strength provided greater lung function effects at day 2, day 112 and day 169, and only the 100 µg-25 µg strength provided greater lung function effects at day 14. Both fluticasone furoate-vilanterol arms showed greater improvements compared to placebo in diary card symptoms, rescue use or rescue-free 24-h periods, nighttime awakenings and morning peak flow. The incidence of on-treatment adverse events was higher with active therapy compared to placebo, but the reports of serious adverse events were similar across arms. Reported adverse events included nasopharyngitis, local steroidal effects (candidiasis, oropharyngeal pain) and upper respiratory tract infection.
Agusti et al.[194] (2013) Fluticasone furoate- vilanterol 100-25 µg QD	DB, DD, MC, PG, RCT Patients aged ≥40 years of age with a smoking	N=528 12 weeks	Primary: 24-hour effect on lung function after 12 weeks assessed by change from baseline in	Primary: On day 84, there was no significant difference in improvement from baseline between the fluticasone propionate-salmeterol (108±221 mL) and fluticasone furoate-vilanterol (130±222 mL) groups (P=0.282). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluticasone propionate-salmeterol 500-50 µg BID	history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and at least one moderate COPD exacerbation within the last 2 years.		weighted mean FEV_1 Secondary: Time to 100 mL increase from baseline from zero to four hours on day one, change from baseline in trough FEV_1 on day 85 and change in health status	Because statistical significance was not achieved for the primary endpoint, statistical significance in the secondary endpoints could not be inferred. The mean change from baseline in trough FEV_1 on day 85 was 88 mL in the fluticasone propionate-salmeterol group compared to 111 mL in the fluticasone furoate-vilanterol (mean treatment different, 23 mL; 95% CI, -21 to 66). The median time to reach an increase of ≥100 mL in FEV_1 was 28 minutes in the fluticasone propionate-salmeterol group compared to 16 minutes in the fluticasone furoate-vilanterol. There was no significant difference in the proportion of rescue free 24-hour periods between the groups. The rate of adverse events was similar between the groups.
Mansori et al.[195] (2010) Salmeterol 50 µg, BID vs fluticasone propionate - salmeterol 250-50 µg, BID All patients received theophylline sustained release 200 mg BID and ipratropium 40 µg QID before starting the trial.	RCT Male COPD patients with FEV_1 <65%, an FEV_1/FVC <70%, >2 COPD exacerbations within the previous 2 years, with a smoking history >20 packs/year but were ex-smokers in the last 2 years	N=40 3 months	Primary: Pulmonary function tests, SABA use, and six minute walk distance Secondary: Not reported	Primary: Changes in six minute walk distance, FVC, FEV_1, PEF and the frequency of using a SABA with fluticasone propionate -salmeterol were significantly greater compared to those receiving salmeterol (P<0.01 to P<0.001). The number of exacerbations during 90 days in the last year before the trial was not statistically different between the two groups; however, the number of exacerbations during the 90 day treatment period in patients treated with fluticasone propionate was significantly lower compared to the other patients (P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ohar et al.[196] (2014) Fluticasone propionate-salmeterol 250-50 µg BID (FP/SAL) vs salmeterol 50µg BID (SAL)	AC, DB, PG, RCT Patients with COPD aged ≥40 years with recent (≤14 days) history of exacerbation requiring: hospitalization for ≤10 days, emergency room observation of duration ≥24 hours during which oral steroids ±antibiotics treatment was administered, or physician's office or emergency room visit of <24 hours duration with steroids ±antibiotics treatment plus 6-month history of exacerbation-related hospitalization	N=639 26 weeks	Primary: Estimated annualized rate of exacerbations requiring hospitalization Secondary: Rate of exacerbations requiring treatment with oral steroids, antibiotics, and/or hospitalization	Primary: There was no statistically significant treatment difference in rates of recurrent severe exacerbations (treatment ratio 0.92 [95% CI, 0.58 to 1.45]) and moderate/severe exacerbations (0.82 [0.64 to 1.06]) between FP/SAL and SAL in the intent-to-treat population. Secondary: Pre-dose morning FEV_1 change from baseline was greater (0.10 L [0.04 to 0.16]) with FP/SAL than SAL. No treatment difference was seen for other endpoints including patient-reported health outcomes and biomarker levels for the full cohort.
Donohue et al.[197] (2015) Fluticasone propionate and salmeterol 250/50 µg inhaled BID vs umeclidinium and	DB, DD, PG, MC, RCT Patients ≥ 40 years of age with a diagnosis of moderate to severe COPD, post-albuterol FEV_1 30 to 70% of predicted, pre and post	Study 1: N=706 12 weeks Study 2: N=697 12 weeks	Primary: 24 hour weighted mean FEV_1 on day 84 Secondary: Trough FEV_1 on day 85 and safety outcomes	Primary: The 24 hour weighted mean FEV_1 improved from baseline in both groups. The LS mean change from baseline was greater in the umeclidinium-vilanterol group than the fluticasone propionate-salmeterol group (Study 1: treatment difference 0.074 L; 95% CI, 0.038 to 0.110; P<0.001; Study 2: treatment difference 0.101 L; 95% CI, 0.063 to 0.139 P<0.001). Secondary: The trough FEV_1 improved from baseline in both groups. The LS mean change from baseline was greater in the umeclidinium-vilanterol group than the fluticasone propionate-salmeterol group (Study 1: treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vilanterol 62.5/25 µg inhaled daily (The results of two studies with the same methodology were reported in one manuscript)	albuterol FEV_1 to FVC ratio <0.70, and ≥ 10 pack-year smoking history without a serious exacerbation in the past year.			difference 0.082 L; 95% CI, 0.045 to 0.119; P<0.001; Study 2: treatment difference 0.098 L; 95% CI, 0.059 to 0.137; P<0.001). Rates of adverse events were similar between treatment groups. Adverse events occurred in 26% of patients (Study 1) and 30% of patients (Study 2) in the umeclidinium-vilanterol group versus 27% of patients (Study 1) and 31% of patients (Study 2) in the fluticasone propionate-salmeterol group. Rates of COPD exacerbations were also similar between groups. COPD exacerbations occurred in 3% of patients in each of the umeclidinium-vilanterol and fluticasone propionate-salmeterol groups in both Study 1 and Study 2.
Dal Negro et al.[198] (2003) Fluticasone propionate - salmeterol 250-50 µg BID vs salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients 53 to 78 years of age with moderate COPD who were naïve to ICS, FEV_1 ≤80% predicted value but >800 mL, FEV_1/ FVC ratio ≤70% predicted value, FEV_1 change of ≤12% following β-agonist administration, receiving regular treatment with oral theophylline 200 mg BID, SABA as needed current or ex-smokers with history of at least 10 pack years	N=18 52 weeks	Primary: FEV_1, morning PEF values, COPD symptom scores, number of exacerbations, and β-agonist use Secondary: Not reported	Primary: Increase in FEV_1 percent predicted noted in fluticasone propionate - salmeterol group but this increase was not significant (49.9 to 53.4%; P=0.07). However, if the increase is expressed as a percent over baseline value, it is significant in the fluticasone propionate -salmeterol group (1.1 to 6.6; P<0.001), but not in the salmeterol group (P=0.79). Statistically significant increase in morning PEF values in fluticasone propionate -salmeterol group compared to placebo (180.0 to 255.4 L/min compared to 18,606.0 to 173.3 L/min; P<0.001), but values did not change in salmeterol and placebo groups. Statistically significant reduction in daily symptom scores in fluticasone propionate -salmeterol group (P=0.008), but not in salmeterol group. Statistically significant reduction in β-agonist use in fluticasone propionate -salmeterol group (4.2 to 1.9; P<0.001), but not in salmeterol group 4.1 to 4.2). Statistically significant decrease in exacerbations in fluticasone propionate -salmeterol group (P<0.001), but not in salmeterol group.
Hanania et al.[199] (2003)	DB, MC, PC, MC, RCT	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and two hour	Primary: Statistically significant increase in pre-dose FEV_1 in fluticasone propionate -salmeterol group compared to the salmeterol group (91 mL;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate - salmeterol 250-50 µg BID vs fluticasone propionate 250 µg BID vs salmeterol 50 µg BID vs placebo	Patients 40 to 87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)		post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, chronic respiratory disease questionnaire, chronic bronchitis symptom questionnaire, exacerbations, and supplemental albuterol use	P=0.012) and placebo (1 mL; P<0.001). No significant difference between fluticasone propionate -salmeterol group and fluticasone propionate group. Statistically significant increase in two hour post-dose FEV_1 in fluticasone propionate -salmeterol group compared to the salmeterol group (281 vs 200 mL; P<0.001), placebo (281 vs 58 mL; P<0.001), and fluticasone propionate group (281 vs 147 mL; P<0.001). Secondary: Statistically significant increase in morning PEF values in fluticasone propionate -salmeterol group compared to the salmeterol group, placebo group, and fluticasone propionate group (P≤0.034), though improvements were also seen from baseline in salmeterol and fluticasone propionate monotherapy groups (P<0.001). Statistically significant improvements in dyspnea index observed in fluticasone propionate -salmeterol group (P=0.023) compared to placebo, in addition to improvements in fluticasone propionate (P=0.057) and salmeterol (P=0.043) monotherapy groups compared to placebo (NOTE: difference in fluticasone propionate monotherapy group not significant). Statistically significant reduction in supplemental albuterol use in fluticasone propionate -salmeterol group compared to fluticasone propionate monotherapy group (-1.0 vs -0.2; P=0.036) and placebo (-1.0 vs 0.1; P=0.002). Numerical reduction in supplemental albuterol use in fluticasone propionate -salmeterol group compared to salmeterol monotherapy group. Statistically significant increase in chronic bronchitis symptom questionnaire scores in fluticasone propionate -salmeterol group and fluticasone propionate monotherapy group compared to placebo (P≤0.017). There was significant difference between treatment groups in terms of exacerbations or time to first exacerbation.
Calverley et al.[200]	DB, PC, PG, RCT	N=1,465	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Fluticasone propionate - salmeterol 500-50 µg BID vs fluticasone propionate 500 µg BID vs salmeterol 50 µg BID vs placebo	Patients with COPD, pre-dose FEV_1 25 to 70% predicted, <10% increase in FEV_1 after β-agonist use, pre-bronchodilator FEV_1/FVC ratio of 70% or less, smoking history of at least 10 pack years, a history of chronic bronchitis, at least 1 COPD exacerbation per year for previous 3 years, and at least 1 exacerbation in previous year requiring oral corticosteroids, antibiotics, or both	12 months	Pre-dose FEV_1 after 12 months of treatment and after abstaining from bronchodilators for at least six hours and from study medication by at least 12 hours Secondary: Pre-dose FVC, post-bronchodilator FEV_1 and FVC, morning PEF, use of relief medication, symptom scores, nighttime awakenings, acute COPD exacerbations, and St. George's Respiratory Questionnaire scores	Statistically significant improvement in pre-dose FEV_1 in all treatment groups compared to placebo (P<0.001 for salmeterol, P=0.0063 for fluticasone propionate, and P<0.001 for fluticasone propionate - salmeterol) and statistically significant improvement in fluticasone propionate -salmeterol group compared to fluticasone propionate and salmeterol monotherapy groups (P<0.001). Secondary: Predose FVC improved significantly in all groups compared to placebo (P=0.0004 for salmeterol, P=0.013 for fluticasone propionate, and P<0.001 for fluticasone propionate -salmeterol) and there was a statistically significant improvement in pre-dose FVC in fluticasone propionate -salmeterol group when compared to fluticasone propionate and salmeterol monotherapy groups (P=0.006 for salmeterol and P<0.001 for fluticasone propionate). Postbronchodilator FEV_1 improved significantly in fluticasone propionate and fluticasone propionate -salmeterol group compared to placebo (P=0.013 for fluticasone propionate and P<0.001 for fluticasone propionate -salmeterol) and there was a statistically significant difference between fluticasone propionate -salmeterol group compared to salmeterol and fluticasone propionate monotherapy (P=0.039 and P=0.0014 respectively). Statistically significant improvement in PEF in all treatment groups compared to placebo (P<0.001), and there was a statistically significant improvement in fluticasone propionate -salmeterol group compared to fluticasone propionate and salmeterol monotherapy (P<0.001). All active treatment groups significantly decreased the number of exacerbations per patient per year compared to placebo (P=0.003) but there was no significant difference between the groups. Statistically significant reduction in the use of relief medication in fluticasone propionate -salmeterol group compared to placebo and other treatment groups (P<0.001 for placebo, P=0.004 for salmeterol, and P=0.003 for fluticasone propionate).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Statistically significant reduction in nighttime awakenings in fluticasone propionate -salmeterol group compared to placebo and salmeterol groups (P=0.006 and P=0.011 respectively) but there was no significant difference between fluticasone propionate -salmeterol and fluticasone propionate monotherapy groups (P=0.591). Fluticasone propionate -salmeterol combination therapy showed significant improvement in St. George's Respiratory Questionnaire scores compared to placebo and fluticasone propionate groups (P=0.0003 and P=0.021 respectively), but no difference between fluticasone propionate -salmeterol and salmeterol monotherapy groups (P=0.071).
Vestbo et al.[201] (2005) Fluticasone propionate -salmeterol 500-50 µg BID vs fluticasone propionate 500µg BID vs salmeterol 50 µg BID vs placebo	DB, PC, PG, RCT Patients with COPD, pre-dose FEV_1 25 to 70% predicted, <10% increase in FEV_1after β-agonist use, pre-bronchodilator FEV_1/FVC ratio of 70% or less, smoking history of at least 10 pack years, history of chronic bronchitis, at least 1 COPD exacerbation per year for previous 3 years, and one of them requiring oral corticosteroids, antibiotics, or both	N=1,465 12 months	Primary: Time to first observation of treatment effects in each arm of study, analyzed for the first 14 days after initial treatment Secondary: Not reported	Primary: Significant increase in PEF in fluticasone propionate -salmeterol and salmeterol monotherapy groups over placebo after one day (P<0.001). This was also observed in the fluticasone propionate group on day two (P<0.001). Increase in PEF values in the fluticasone propionate -salmeterol group was significantly better than the other treatment arms after day one (P<0.001). No other mention of comparison between groups. Significant increase in FEV_1 values in all treatment arms compared to placebo by day 14 (P<0.001 for salmeterol monotherapy and fluticasone propionate -salmeterol groups and P=0.016 for fluticasone propionate monotherapy group). No mention of comparison between groups. Secondary: Not reported
Calverley et al.[202] (2007)	DB, MC, PC, PG, RCT	N=6112	Primary: Death from any	Primary: The proportions of deaths from any cause at three years were 12.6% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluticasone propionate - salmeterol 500-50 µg BID vs salmeterol 50 µg BID vs fluticasone propionate 500 µg BID vs placebo	Patients 40 to 80 years of age with COPD, current or former smokers, ≥10 pack-year history, pre bronchodilator FEV_1 <60% of predicted value, an increase of FEV_1 <10% of predicted value with use of 400 µg of albuterol, and FEV1/FVC ratio of ≤0.70	3 years	cause Secondary: Frequency of SAE, defined as a symptomatic deterioration requiring treatment with antibiotics, systemic corticosteroids, hospitalization, or a combination of the above; health status accessed via the St. George's Respiratory Questionnaire; lung function as accessed via post-bronchodilator spirometry ; adverse events and safety	combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone propionate group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6% (HR, 0.825; 95% CI, 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, 0.2 to 31.9). The risk of death in the salmeterol group and in the fluticasone propionate group did not differ significantly from that in the placebo group, and was similar among patients who died while receiving a study medication. The risk of death in the combination-therapy group did not differ significantly from that in the salmeterol group, but patients receiving the combination regimen were less likely to die than those receiving fluticasone propionate (HR, 0.774; 95% CI, 0.641 to 0.934; P=0.007). Secondary: Annual rate of exacerbations was 0.85 (95% CI, 0.80 to 0.90) in the combination-therapy group and 1.13 (95% CI, 1.07 to 1.20) in the placebo group, a rate ratio for exacerbations of 0.75 (95% CI, 0.69 to 0.81; P<0.001), a reduction of 25% and corresponding to a NNT of four to prevent one exacerbation in one year. Annual rates of exacerbations in the salmeterol group and the fluticasone propionate group were significantly lower than in the placebo group. Overall, 26% of the patients were hospitalized at least once during the three-year study period. Annual admission rates were 17% lower in the combination-therapy and salmeterol groups than in the placebo group (P=0.03), corresponding to a NNT of 32 to prevent one hospitalization in one year. Total scores on the St. George's Respiratory Questionnaire initially improved from baseline in all groups, with the greatest changes occurring in the combination-therapy group (mean score at baseline, 48.7, with a mean reduction of 3.0 units averaged over three years), as compared with the placebo group (a mean score of 48.4 at baseline, with an increase of 0.2 unit in the placebo group). For lung function, the mean baseline FEV_1 in the combination-therapy group was 1.236 liters with an average increase of 0.029 liter; in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo group, the mean baseline FEV_1 was 1.257 liters and a decrease of 0.062 liter. Averaged over three years, the health status (a reduction of 3.1 units in the score for the St. George's Respiratory Questionnaire) and spirometric measurements (an increase in FEV_1 of 0.092 liter) in the combination-therapy group were significantly better than in the groups receiving placebo, salmeterol alone, or fluticasone propionate alone). The most frequently reported adverse event was an exacerbation of COPD. The probability of having pneumonia reported as an adverse event during the three-year study period was significantly greater among patients receiving a study medication containing fluticasone propionate: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone propionate group (P<0.001 for the comparison between both the combination-therapy and fluticasone propionate groups and the placebo group). There was no significant difference in the probability of fractures among the groups. There was no excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone. In the safety substudy, there were no significant differences in bone mineral density or in the numbers of patients in whom cataracts developed.
Raphael et al.[203] (2017) Fluticasone propionate multidose DPI 50 or 100 µg twice daily vs fluticasone propionate-salmeterol	DB, MC, PG, PC, RCT Patients ≥12 years of age with a diagnosis of persistent asthma with a FEV1 ≥40% and ≤85% o predicted value for age, height, sex and race	N=647 12 weeks	Primary: Change from baseline in trough FEV_1 at week 12 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after dosing at week 12 in a subset of patients	Primary: At week 12, significant improvements from baseline in trough FEV_1 were observed in the fluticasone 50 and 100 µg and fluticasone-salmeterol 50-12.5 and 100-12.5 µg treatment groups compared with the placebo group (P<0.05). At week 12, the fluticasone-salmeterol 50-12.5 µg group demonstrated significant improvements from baseline in FEV_1 compared with the fluticasone 50 µg group (P<0.05), and both fluticasone-salmeterol 50-12.5 µg and 100-12.5 µg treatment groups demonstrated significant improvements compared with the fluticasone 100 µg treatment group (P≤0.05). In the serial spirometry subset of patients, standardized baseline-adjusted FEV_1 area under the effect curve from time 0 to 12 hours was significantly improved at week 12 compared with placebo for the fluticasone 50 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mutldose DPI 50-12.5 µg or 100-12.5 µg twice daily vs placebo			performing serial spirometry after dosing Secondary: Change from baseline in weekly averages of the daily trough morning PEF, total daily asthma symptom score, total daily rescue medication use, the time to patient withdrawal due to worsening asthma, the change from baseline to endpoint in the AQLQ and time to 15% and 12% improvement from baseline in FEV_1 after dosing on day 1 over 12 weeks	100 µg and fluticasone-salmeterol 50-12.5 and 100-12.5 µg groups (P≤0.05). Secondary: Patients treated with fluticasone-salmeterol 50-12.5 µg and fluticasone-salmeterol 100-12.5 µg experienced greater improvements in weekly average of daily trough morning PEF compared with patients treated with fluticasone 50 µg and both fluticasone 50 and 100 µg, respectively (P≤0.05). In addition, improvements in morning PEF for patients in the fluticasone 100 µg and both fluticasone-salmeterol treatment groups were significantly greater compared with the placebo group (P≤0.05). Changes from baseline in weekly averages of the total daily asthma symptom scores, in total daily use of albuterol/salbutamol, and in the AQLQ(S) score were similar between the fluticasone and flucticasone-salmeterol groups and significantly greater than placebo (P≤0.05). The times to patient withdrawal for worsening asthma symptoms were similar between fluticasone and flucticasone-salmeterol groups, and were also similar between fluticasone groups and fluticasone-salmeterol 50-12.5 µg group and the placebo group due to few withdrawals. In the serial spirometry subset, the comparison between active treatment groups demonstrated that the proportions of patients who met the predefined thresholds of 15% and 12% improvements from baseline in FEV_1 postdose at day 1 were greater in the fluticasone-salmeterol treatment groups vs the corresponding fluticasone treatment groups. In addition, the proportions of patients with time to 15% and 12% improvements from baseline in FEV_1 postdose were greater for both fluticasone doses compared with placebo. The time to improvement in the fluticasone-salmeterol groups was significantly greater than that in the placebo group for 15% improvement (P<0.05) and for 12% improvement (P<0.0001).
Mansfield L.[204] (2017) Mid-strength	OL, RCT Patients ≥12 years of age with FEV_1 of	N=674 6 months	Primary: Incidence and type of adverse reactions	Primary: Overall, 463 subjects (69%) experienced at least one treatment emergent adverse event during the study. The incidences of treatment emergent adverse event, treatment-related treatment emergent adverse event, serious

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate multidose DPI 100 µg or fluticasone propionate HFA 220 µg twice daily vs high-strength fluticasone propionate multidose DPI 200 µg or fluticasone HFA 440 µg vs mid-strength fluticasone-salmeterol multidose DPI 100-12.5 µg or fluticasone-salmeterol DPI 250-50 µg vs high-strength fluticasone-salmeterol multidose DPI 200-12.5 µg or fluticasone-salmeterol DPI 500-50 µg	≥40% of predicted value for age, height, sex, and race, an established treatment regiment of a SABA for use as needed and either a mid- or high-dose ICS or ICS/ALBA combination as preventive therapy for ≥8 weeks before the screening visit, demonstrated ≥12% reversibility of FEV_1 within 30 minutes after SABA HFA 90 µg administration at the screening visit, and the ability to replace existing SABA with albuterol/ salbutamol HFA at screening for as-needed use during the study		Secondary: Change from baseline in morning trough FEV_1 over 26 weeks, change from baseline in FVC and FEF between 25% and 75%, frequency and amount of rescue medication use, change in morning PEF, change from baseline in asthma symptom scores and withdrawals due to worsening asthma symptoms	treatment emergent adverse event, and treatment emergent adverse events that led to withdrawal were balanced within each treatment and dose cohort, with no evidence of dose or treatment dependence. The most frequently occurring TEAEs across all the treatment groups were upper respiratory tract infections (N=120), nasopharyngitis (N=77), sinusitis (N=62), cough (N=55), and oropharyngeal pain (N=45). Secondary: Noninferiority was established for all fluticasone multidose DPI and fluticasone-salmeterol multidose DPI doses compared with fluticasone HFA and fluticasone-salmeterol DPI doses, respectively, for FEV_1. All pulmonary function variables (FEV_1, FVC, and FEF between 25% and 75%) were comparable between the fluticasone multidose DPI and fluticasone HFA treatment groups and between the fluticasone-salmeterol multidose DPI and fluticasone-salmeterol DPI treatment groups. Sixty three subjects used rescue medication over the 26-week treatment period. The proportion of subjects who used rescue medication was similar among the fluticasone multidose DPI and fluticasone-salmeteriol multidose DPI treatment groups and their respective comparator treatment groups. The subjects within the ICS and ICS/LABA groups experienced similar increases in morning PEF when treated with fluticasone multidose DPI, fluticasone HFA, fluticasone-salmeterol multidose DPI, and fluticasone-salmeterol DPI. Changes from baseline in the asthma symptom scores were similar between the fluticasone multidose DPI groups and comparator fluticasone HFA groups and between the fluticasone-salmeterol multidose DPI groups and comparator fluticsasone-salmeterol DPI groups. Four subjects withdrew from the study due to worsening asthma symptoms during the 26-week treatment period (one subject in the fluticasone multidose DPI 100 µg group, two in the fluticasone-salmeterol multidose DPI 200-12.5 µg group, and one in the fluticasone-salmeterol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				DPI 500-50 µg group).
Sher et al.[205] (2017) Fluticasone propionate multidose DPI 100 µg twice daily vs fluticasone priopionate multidose DPI 200 µg twice daily vs fluticasone propionate-salmeterol multidose DPI 100-12.5 µg twice daily vs fluticasone propionate-salmeterol multidose DPI 200-12.5 µg twice daily vs placebo	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma, FEV_1 of ≥40% and ≤85% of predicted value for age, heigh, sex and race, exhibited ≥15% reversibility in FEV_1 and ≥200 mL increase in FEV_1 from baseline within 30 minutes of exposure to a SABA, and had a treatment regimen that included albuterol or salbutamol for use as needed for ≥8 weeks before screening and an ICS at a qualifying dose for ≥1 month	N=782 12 weeks	Primary: Change from baseline in trough FEV_1 at week 12 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after the dose at week 12 Secondary: Changes from baseline in the weekly average of the daily trough morning PEF value, total daily asthma symptom score and total daily albuterol HFA MDI use, time to patient withdrawal due to worsening asthma, change from baseline in AQLQ score among patients ≥18 years of age and time to 15% and 12% improvement from baseline in FEV_1	Primary: The improvement from baseline in the trough FEV_1 at week 12 was significantly greater in patients treated with fluticasone-salmeterol multidose DPI 100 µg-12.5 µg compared with those treated with fluticasone multidose DPI 100 µg and fluticasone multidose DPI 200 µg, and with fluticasone-salmeterol multidose DPI 200-12.5 µg compared with fluticasone multidose DPI 200 µg. Significant improvements in trough FEV_1 at week 12 were also observed in patients treated with fluticasone multidose DPI 100 µg and 200 µg and with fluticasone-salmeterol multidose DPI 100-12.5 µg and 200-12.5 µg compared with placebo ($P<0.05$). Improvements in the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours at week 12 in the serial spirometry subset were significantly greater in the fluticasone-salmeterol multidose DPI 100-12.5 µg group compared with the fluticasone multidose DPI 100 µg and fluticasone multidose DPI 200 µg groups, and in the fluticasone-salmeterol multidose DPI 200-12.5 µg group compared with the fluticasone multidose DPI 200 µg group. Secondary: The improvement in the weekly average of the daily trough morning PEF value was significantly greater in patients treated with fluticasone-salmeterol multidose DPI 100-12.5 µg compared with those treated with fluticasone multidose DPI 100 µg and fluticasone multidose DPI 200 µg, and with fluticasone-salmeterol multidose DPI 200-12.5 µg compared with fluticasone multidose DPI 200 µg (all $P<0.05$). The improvement in daily asthma symptom score was greater in patients treated with fluticasone-salmeterol multidose DPI 100-12.5 µg and fluticasone-salmeterol multidose DPI 200-12.5 µg compared with those treated with fluticasone multidose DPI 200 µg (all $P<0.05$). Decreases in the total daily albuterol use were greater in the fluticasone-salmeterol multidose DPI 100-12.5 µg treatment group compared with the fluticasone multidose DPI 100 µg treatment group and for the fluticasone-salmeterol multidose DPI 200-12.5 µg treatment group compared with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			after the dose at randomization visit in the serial spirometry subset	fluticasone multidose DPI 200 µg treatment group (all P<0.05). Twenty-nine patients withdrew from the study due to worsening asthma, including 20 patients in the placebo group. The time to withdrawal due to worsening asthma did not differ between the fluticasone-salmeterol multidose DPI and fluticasone multidose DPI groups; however, it was significantly greater in each active group compared with the placebo group (all P<0.05). Improvements from baseline in the AQLQ score at the end point in adult patients were significantly greater with fluticasone-salmeterol multidose MDPI 100-12.5 µg compared with fluticasone multidose DPI 100 µg and fluticasone multidose PDI 200 µg (P<0.05). Improvements in AQLQ scores from baseline to the end point were significantly greater for all active treatments versus placebo (P<0.05). The percentage of patients who met the time to 15% and 12% improvement from baseline in FEV_1 after the first dose of study medication on day 1 was greater in the fluticasone-salmeterol multidose DPI groups than in the other groups. Of the patients in the fluticasone-salmeterol multidose DPI 100-12.5 µg group, 21% and 29% achieved a 15% and 12% improvement by 15 minutes after the dose, respectively. Similarly, 34% and 38% of patients in the fluticasone-salmeterol multidose DPI 200-12.5 µg group achieved a 15% and 12% improvement by 15 minutes after the dose, respectively.
Kern et al.[206] (2015) Budesonide and formoterol 160/4.5 µg vs fluticasone and salmeterol 250/50 µg	Retrospective cohort study using claims data from a US managed care database Patients ≥40 years of age naïve to ICS/LABA therapy beginning treatment with one of the study inhalers.	N= 10,227 12 months from index date (index date= date of first study inhaler fill)	Primary: COPD exacerbation rate Secondary: Time to first exacerbation, healthcare resource utilization, rates of any diagnosis of pneumonia, and pneumonia-related	Primary: The rate of COPD exacerbations was no different for patients initiating budesonide-formoterol (exacerbation rate=0.88) or fluticasone-salmeterol (exacerbation rate=0.86) during the 12 months following the initiation of therapy (risk reduction, 1.02, 95% CI,0.96 to 1.09; P= 0.56). Overall, 48% of patients in the budesonide-formoterol group and 47% of patients in the fluticasone-salmeterol group experienced at least one COPD exacerbation during the follow-up period. Patients in the budesonide-formoterol and fluticasone-salmeterol groups had similar rates of COPD-related inpatient hospitalizations (risk reduction, 0.96; 95% CI, 0.79 to 1.16; P=0.66); COPD-related ED

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Patients had to have a primary diagnosis of COPD and continuous plan enrollment for 12 months prior to and 12 months after the index date.		healthcare resource utilization.	visits (risk reduction, 1.11; 95% CI, 0.97 to 1.28; P=0.13); and oral corticosteroid/antibiotics filled within 10 days of a COPD outpatient/office visit (risk reduction, 1.01; 95% CI, 0.94 to 1.09; P=0.72). Secondary: The analysis of time to first exacerbation was consistent with that of the exacerbation rates (HR, 1.03; 95% CI, 0.96 to 1.10; P=0.45), in that there were no differences between groups in risk of COPD exacerbation. Use of healthcare resources was similar between the two cohorts during the 12-month post-index period. A total of 6.2% of patients in the budesonide-formoterol group and 6.9% of patients in the fluticasone-salmeterol group had at least one COPD-related hospitalization (OR, 0.9; 95% CI, 0.76 to 1.10). There was no statistically significant difference between treatment groups in percent of patients with a COPD-related ED or outpatient visit. The proportion of patients diagnosed with pneumonia during the 12 months following the initiation of therapy was similar for patients in the budesonide/formoterol and fluticasone/salmeterol groups (17.3 and 19.0%, respectively; OR, 0.92; 95% CI, 0.81 to 1.04; P=0.19). The percentage of patients with a pneumonia-related inpatient admission, ED visit, or outpatient visit was not statically significant between cohorts.
Rennard et al.[207] (2009) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI vs budesonide-formoterol 80-4.5 µg, 2 inhalations BID via MDI	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a mean percent predicted FEV_1 at baseline ranging from 33.7 to 35.5%	N=1,964 12 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1 Secondary: Improvement in morning and evening PEF, exacerbation rates, BCS scores, sleep scores, awakening	Primary: The budesonide-formoterol 160-4.5 µg treatment group, demonstrated significantly greater improvements in pre-dose and one hour post-dose FEV_1 when compared to the formoterol monotherapy group (P≤0.023). Secondary: Both budesonide-formoterol dose treatment groups had significantly greater improvements in morning and evening PEF when compared to both the formoterol and placebo treatment groups (P≤0.017). Exacerbation rates were significantly reduced by 25 to 30% in both the budesonide-formoterol dose treatment groups when compared to the formoterol treatment group, and by 40% when compared to placebo (P≤0.004). Both budesonide-formoterol treatment groups had significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs formoterol 4.5 µg, 2 inhalations BID via DPI vs placebo			free nights, use of rescue medications, and safety	greater improvements in the sleep score and rescue medication when compared to the formoterol treatment group (P<0.038). Only the budesonide-formoterol 160-4.5 µg treatment group had a significantly greater improvement in the BCS scores compared to the formoterol treatment group (P value not reported), and only the budesonide-formoterol 80/4.5 µg treatment group had a significant improvement in the awakening-free nights compared to formoterol (P<0.038). Both budesonide-formoterol were well tolerated compared to both formoterol and placebo. The incidence of pneumonia related adverse events were similar for all active treatment arms, when compared to placebo. The most common adverse events seen in the budesonide-formoterol treatment groups were oral candidiasis, dysphonia and muscle spasms.
Tashkin et al.[208] (2008) Budesonide-formoterol 160-4.5 µg, 2 inhalations BID via MDI vs budesonide-formoterol 80-4.5 µg 2 inhalations BID via MDI vs budesonide 160 µg, 2 inhalations	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a mean percent predicted FEV_1 at baseline ranging from 33.5 to 34.7%	N=1,704 6 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1 Secondary: Improvement in morning and evening PEF, BCS scores, sleep scores, awakening free nights, use of rescue medications when compared to placebo, and safety	Primary: The budesonide-formoterol 160-4.5 µg treatment group demonstrated a significantly greater improvement from baseline in pre-dose FEV_1 (0.08 L, 10.7%) when compared to the formoterol monotherapy group (0.04 L, 6.9%; P=0.026) and placebo group (0.01, 2.2%; P value not reported). Patients receiving the budesonide-formoterol 80-4.5 µg combination therapy did not report a significantly greater improvement in pre-dose FEV_1 when compared to the formoterol monotherapy group. Both combination budesonide/formoterol treatment arms demonstrated a significantly greater improvement in pre-dose FEV_1 and one hour post-dose FEV_1 when compared to the budesonide monotherapy treatment arm (P<0.001). The budesonide-formoterol 160-4.5 µg treatment group demonstrated a significantly greater improvement from baseline in one hour post-dose FEV_1 (0.20 L, 22.6%; P value not reported) when compared to the budesonide monotherapy group (0.03 L, 4.9%; P<0.001) and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID via MDI and formoterol 4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg 2 inhalations BID via MDI vs formoterol 4.5 µg 2 inhalations BID via DPI vs placebo				(0.03 L, 4.1%; P value not reported). Secondary: Improvements in both morning and evening PEF values were significantly greater in both budesonide-formoterol combination treatment arms, when compared to the budesonide monotherapy, formoterol monotherapy and placebo groups (P≤0.016). Both budesonide-formoterol treatment groups significantly improved BCS scores, sleep scores, awakening free nights and use of rescue medications when compared to placebo (P<0.028). Both budesonide-formoterol treatment doses were well tolerated for the six months of treatment. The most common adverse events reported were oral candidiasis, dysphonia and headache. The incidences of pneumonia-related adverse events were similar across for all active treatment groups compared to placebo.
Ferguson et al.[209] (2017) RISE Budesonide/ formoterol 320/9 µg BID pressurized metered-dose inhaler vs formoterol 9 µg BID dry powder inhaler	DB, DD, MC, RCT Patients ≥40 years of age with moderate-to-very-severe COPD and a history of ≥1 COPD exacerbation within a year before screening and a smoking history of ≥10 pack years	N=1,219 6 months	Primary: Annual rate of COPD exacerbations Secondary: Time to first exacerbation, change from baseline in for predose FEV_1, SGRQ score, nighttime awakenings due to COPD, safety	Primary: Budesonide/formoterol resulted in a 24% reduction in annual rate of exacerbations (0.85 vs 1.12; rate ratio, 0.76; 95% CI, 0.62 to 0.92; P=0.006). Secondary: Time to first exacerbation showed a reduction in risk of 22% with budesonide/formoterol versus formoterol (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.0164). Budesonide/formoterol treatment resulted in a statistically significant difference in predose FEV_1 (P=0.0091)) and reduction in the percentage of nighttime awakenings from baseline to treatment average (P=0.0048) compared with formoterol. SGRQ score was improved in patients treated with budesonide/formoterol vs formoterol (P=0.0070). The most commonly reported adverse events (≥3%) in budesonide/formoterol and formoterol groups were COPD (4.5% vs 8.6%) and nasopharyngitis (5.0% vs 5.2%). Pneumonia adverse events were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported in 0.5% and 1.0% of budesonide/formoterol-treated and formoterol-treated patients, respectively.
Lindberg et al.[210] (2007) Budesonide-formoterol 160-4.5 µg vs fluticasone propionate -salmeterol 250-25 µg vs salbutamol 100 µg vs placebo	DB, DD, MC, RCT, XO Patients ≥40 years of age with COPD and FEV_1 30 to 70% predicted	N=90 17 days	Primary: Change in FEV_1 five minutes after drug inhalation Secondary: Change in FEV_1 at three minutes and 180 minutes; maximal change in FEV_1; change in inspiratory capacity at 15 minutes; maximal change in inspiratory capacity and average effect on inspiratory capacity during observation interval; yes or no answer by patient to perception of onset of effect question; adverse events	Primary: Budesonide-formoterol improved FEV_1 at five minutes to a greater extent than either fluticasone propionate -salmeterol (ratio, 105%; 95% CI, 103 to 108; P=0.0001) or placebo (ratio, 116%; 95% CI, 113 to 119; P<0.0001) and to a similar extent as salbutamol (ratio, 99%; 95% CI, 97 to 101; P=0.35). Secondary: Findings similar to above were observed for FEV_1 at three minutes. Compared with placebo, FEV_1 was significantly improved over 180 minutes after all three active treatments (all P<0.0001), although improvements were maintained more effectively with budesonide-formoterol and fluticasone propionate -salmeterol than with salbutamol, as demonstrated by FEV_1 at 180 minutes, ratio 107% (95% CI, 104 to 109) for budesonide-formoterol and 106% (95% CI, 103 to 108) for fluticasone propionate -salmeterol vs salbutamol; both P<0.0001). Maximal increases in FEV_1 were 0.35, 0.32, 0.34 and 0.14 L for budesonide-formoterol, fluticasone propionate -salmeterol, salbutamol and placebo respectively, with no statistically significant differences among the three active treatments in maximal FEV_1 or average FEV_1 over 180 minutes. All three active treatments were superior to placebo for both variables (all P<0.0001). IC was significantly improved at 15 minutes following all three active treatments compared with placebo (all P<0.0001), with no significant differences among the active treatments. Maximal increases in IC were 0.65, 0.53, 0.54 and 0.28 L for budesonide-formoterol, fluticasone propionate -salmeterol, salbutamol and placebo respectively, representing a 4% greater increase for budesonide-formoterol vs fluticasone propionate -salmeterol (ratio, 104; 95% CI, 101 to 107; P=0.0184) and a 13% greater increase vs placebo (ratio, 113%; 95% CI, 110 to 117; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no differences between the active treatments in average inspiratory capacity over 185 minutes. The effect of budesonide-formoterol and fluticasone propionate -salmeterol on inspiratory capacity was of longer duration than that of salbutamol. Perception of onset of effect: The proportion of patients answering 'yes' to the question regarding whether they felt their medication working was 84, 81, 84 and 61% following treatment with budesonide-formoterol, fluticasone propionate -salmeterol, salbutamol and placebo, respectively. Time to perception of onset of effect was 10 minutes faster (95% CI, -75.0, -3.5) for budesonide-formoterol and 10.5 minutes faster (95% CI, -80.0, -3.5) for salbutamol compared with placebo; time to perception of onset of effect was slightly slower with fluticasone propionate -salmeterol, being observed five minutes faster (95% CI, -75.0 to 0.0) than placebo All active treatments resulted in a significantly faster time to perception of onset of effect than placebo (all P<0.001). Median time to perception of onset of effect was five minutes for each of the three active treatments and 20 minutes for placebo, with no statistically significant differences among active treatments. All treatments were well tolerated and no new or unexpected safety concerns were identified. There were 24 adverse events in total, all mild to moderate, of which none was considered to be related to study treatment. No serious adverse events or deaths were reported, nor were clinically important differences between treatments, changes over time or abnormalities reported with respect to vital signs and physical findings.
Larsson et al.[211] (2013) Budesonide-formoterol vs	OS, RETRO Patients with COPD	N=9,893 Duration not reported	Primary: COPD exacerbations, emergency visits, utilization of steroids or antibiotics and utilization of other	Primary: The COPD exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide-formoterol and fluticasone propionate-salmeterol treatment groups, respectively, representing a 26.6% reduction in exacerbation rate in the budesonide-formoterol group (rate ratio, 0.74; 95% CI, 0.69 to 0.79; P<0.0001). This corresponded to a NNT of 3.4 with budesonide-formoterol compared to fluticasone propionate-salmeterol to prevent one exacerbation per patient-year.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluticasone propionate-salmeterol			medications used in managing COPD Secondary: Not reported	In budesonide-formoterol-treated patients, the yearly rate of COPD-related hospitalizations was 0.15 compared to 0.21 in patients treated with fluticasone propionate-salmeterol (P<0.0001), a difference of 29.1% (rate ratio, 0.71; 95% CI, 0.65 to 0.78; P<0.0001). The NNT to prevent one COPD-related hospitalization per patient-year was 16 with budesonide-formoterol compared to fluticasone propionate-salmeterol. There were 27% fewer days in the hospital due to exacerbations of COPD with budesonide-formoterol compared to fluticasone propionate-salmeterol (0.63 vs 0.95 days/year; rate ratio, 0.66; 95% CI, 0.62 to 0.71; P<0.0001). There were 21% fewer emergency visits in the budesonide-formoterol treatment group compared to the fluticasone propionate-salmeterol group (0.027 vs 0.034 events/patient-year; rate ratio, 0.79; 95% CI, 0.71 to 0.89; P=0.0003). Patients treated with budesonide-formoterol experienced 26% fewer courses of oral steroids (0.63 vs. 0.85 events per year; rate ratio, 0.74; 95% CI, 0.68 to 0.81; P<0.0001) and 29% fewer antibiotic courses (0.38 vs. 0.54 events per year; rate ratio, 0.70; 95% CI, 0.66 to 0.75; P<0.0001) than patients treated with fluticasone propionate-salmeterol. The number of patients who required tiotropium in addition to the ICS/LABA combination was 16% lower for the budesonide-formoterol group compared to fluticasone propionate-salmeterol group (rate ratio, 0.84; 95% CI, 0.79 to 0.89; P<0.0001). Secondary: Not reported
Welte et al.[212] (2009) Budesonide-formoterol 320-9 µg BID and tiotropium 18 µg QD	DB, MC, PG, RCT Patients >40 years of age with COPD and FEV_1<50%	N=660 12 weeks	Primary: Pre- and postdose FEV_1, pre- and postdose FVC and inspiratory capacity, health status	Primary: Budesonide-formoterol treatment significantly increased pre- and postdose FEV_1 by 6 and 11%, respectively compared to tiotropium alone (P<0.001). Secondary: SGRQ-C total score improved by 3.8 units in the budesonide-formoterol group compared to 1.5 units in the tiotropium monotherapy group (mean difference, -2.3; 95% CI, -4.23 to 0.32; P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tiotropium 18 µg QD			Secondary: PEF, morning symptoms and activities, morning reliever use, exacerbations, tolerability	Morning PEF and FEV_1 were improved with budesonide-formoterol therapy compared to tiotropium monotherapy as early as week one, and maintained statistically significant to week 12 (P<0.001 for all weeks). Morning symptoms and activities were significantly better in the budesonide-formoterol group compared to the tiotropium group (P<0.001). There were significant improvements in reliever medication in the budesonide-formoterol group. A total of 7.6% of patients in the budesonide-formoterol group experienced exacerbations compared to 18.5% in the tiotropium group (RR, 0.38; 95% CI, 0.25 to 0.57; P<0.001). Hospitalizations and emergency department visits were decreased by 65% in the budesonide-formoterol group compared to the tiotropium group (RR, 0.35; 95% CI, 0.16 to 0.78; P=0.011). There were no differences in tolerability between the regimens.
Ferguson et al.[213] (2018) KRONOS Budesonide-glycopyrrolate-formoterol MDI 320-18-9.6 µg two inhalations BID vs glycopyrrolate-formoterol MDI 18-9.6 µg two inhalations BID	DB, MC, PG, RCT Patients 40 to 80 years of age, were current or former smokers (with a smoking history of ≥10 pack-years), had an established clinical history of COPD, and were symptomatic for COPD, despite receiving two or more inhaled maintenance	N=1,902 24 weeks	Primary: FEV_1 area under the curve from 0 to 4 hours and change from baseline in morning pre-dose trough FEV_1 over 24 weeks Secondary: Change from baseline in morning pre-dose trough FEV1, peak change from baseline in FEV1	Primary: Budesonide-glycopyrrolate-formoterol MDI significantly improved FEV_1 area under the curve from 0 to 4 hours versus budesonide-formoterol MDI (LSM difference, 104 mL; 95% CI, 77 to 131; P<0.0001) and budesonide-formoterol DPI (LSM difference, 91 mL; 95% CI, 64 to 117; P<0.0001). The change from baseline in morning pre-dose trough FEV_1 over 24 weeks was significantly improved by budesonide-glycopyrrolate-formoterol MDI vs glycopyrrolate-formoterol MDI (LSM difference, 22 mL; 95% CI, 4 to 39; P=0.0139) and budesonide-formoterol MDI (LSM difference, 74 mL; 95% CI, 52 to 95 mL; P<0.0001). Budesonide-formoterol MDI was non-inferior to budesonide-formoterol DPI for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks (LSM difference, -10 mL; 95% CI, -36 to 16; P=0.4390) At week 24, patients in the budesonide-glycopyrrolate-formoterol MDI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs budesonide-formoterol MDI 320-9.6 µg two inhalations BID vs budesonide-formoterol DPI 400-12 µg two inhalations BID (open label)	therapies for at least six weeks before screening		within 4 hours after dosing, rate of moderate or severe COPD exacerbations, TDI focal score, change from baseline in SGRQ total score, E-RS:COPD total score, time to clinically important deterioration, and change from baseline in daily rescue medication use all over 24 weeks	group had a significantly improved FEV_1 area under the curve from 0 to 4 hours compared with patients receiving budesonide-formoterol MDI (LSM difference, 116 mL; 95% CI, 80 to 152; P<0.0001). Secondary: There was a non-significant improvement in the change from baseline in morning pre-dose trough FEV_1 at week 24 in the budesonide-glycopyrrolate-formoterol MDI versus glycopyrrolate-formoterol MDI group (LSM difference, 13 mL; 95% CI, -9 to 36; P=0.2375). Budesonide-glycopyrrolate-formoterol MDI significantly increased peak change from baseline in FEV_1 over 24 weeks versus budesonide-formoterol MDI (LSM difference, 105 mL; 95% CI, 78 to 133; P<0.0001), but not vs glycopyrrolate-formoterol MDI. The model-estimated rates of moderate or severe exacerbations were 0.46 per year for budesonide-glycopyrrolate-formoterol MDI, 0.95 per year for glycopyrrolate-formoterol MDI, 0.56 per year for budesonide-formoterol MDI and 0.55 per year for budesonide-formoterol DPI. The rate of moderate or severe exacerbations was significantly lower during treatment with budesonide-glycopyrrolate-formoterol MDI versus glycopyrrolate-formoterol MDI. Budesonide-glycopyrrolate-formoterol MDI reduced the rate of moderate or severe exacerbations compared with budesonide-formoterol MDI and budesonide-formoterol DPI, but these reductions were not significant. Budesonide-glycopyrrolate-formoterol MDI significantly improved TDI focal score versus budesonide-formoterol DPI, but not versus glycopyrrolate-formoterol MDI and budesonide-formoterol MDI, and provided nominally significant improvements in change from baseline in RS-Total score over 24 weeks versus glycopyrrolate-formoterol MDI but not budesonide-formoterol MDI or budesonide-formoterol DPI. Budesonide-glycopyrrolate-formoterol MDI also resulted in nominally significant improvements in SGRQ total score over 24 weeks versus glycopyrrolate-formoterol MDI but not budesonide-formoterol MDI or budesonide-formoterol DPI. Time to clinically important deterioration was nominally significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reduced by budesonide-glycopyrrolate-formoterol MDI versus budesonide-formoterol MDI and budesonide-formoterol DPI, but there was no difference compared with glycopyrrolate-formoterol MDI. There was no significant difference between groups in the average puffs per day of daily rescue medication.
Rabe et al.[214] (2020) ETHOS Budesonide-glycopyrrolate-formoterol 320-18-9.6 µg two inhalations BID vs budesonide-glycopyrrolate-formoterol 160-18-9.6 µg two inhalations BID vs glycopyrrolate-formoterol 18-9.6 µg two inhalations BID vs budesonide-formoterol 320-9.6 µg two inhalations BID	DB, MC, PG, RCT Patients 40 to 80 years of age and had symptomatic COPD, were receiving at least two inhaled maintenance therapies at the time of screening, had a postbronchodilator $FEV_1/FVC<0.7$ with a postbronchodilator FEV_1 of 25 to 65% of the predicted normal value; had a smoking history of at least 10 pack-years, and had a documented history of at least one moderate or severe COPD exacerbation or at least two moderate or at least one severe COPD exacerbation in the year before screening.	N=8,509 52 weeks	Primary: Annual rate of moderate or severe COPD exacerbations Secondary: Time to the first moderate or severe COPD exacerbation, the annual rate of severe COPD exacerbations and time to death from any cause.	Primary: The model-estimated annual rates of moderate or severe exacerbations were 1.08 in the 320 µg budesonide triple-therapy group, 1.07 in the 160 µg budesonide triple-therapy group, 1.42 in the glycopyrrolate-formoterol group and 1.24 in the budesonide-formoterol group. The annual rate of moderate or severe exacerbations was significantly lower with 320 µg budesonide triple therapy than with glycopyrrolate-formoterol (24% lower; rate ratio, 0.76; 95% CI, 0.69 to 0.83; P<0.001) or budesonide–formoterol (13% lower; rate ratio, 0.87; 95% CI, 0.79 to 0.95; P=0.003). The annual rate of moderate or severe exacerbation was significantly lower with 160 µg budesonide triple therapy than with glycopyrrolate-formoterol (25% lower; rate ratio, 0.75; 95% CI, 0.69 to 0.83; P<0.001) or budesonide-formoterol (14% lower; rate ratio, 0.86; 95% CI, 0.79 to 0.95; P=0.002). No difference was observed between the two triple-therapy groups (rate ratio, 1.00; 95% CI, 0.91 to 1.10). Secondary: Both triple-therapy regimens significantly prolonged the time to the first moderate or severe exacerbation as compared with both dual therapies. The model-estimated annual rates of severe exacerbations were 0.13 in the 320 µg budesonide triple-therapy group, 0.14 in the 160 µg budesonide triple-therapy group, 0.15 in the glycopyrrolate-formoterol group, and 0.16 in the budesonide-formoterol group. The risk of death from any cause in the final retrieved dataset was significantly lower with 320 µg budesonide triple-therapy group relative to glycopyrrolate-formoterol group (HR, 0.51; 95% CI, 0.33 to 0.80; 49% reduction; unadjusted P=0.0035), equivalent to a number needed to treat of 80 (95% CI, 58 to198). The 320 µg budesonide triple-therapy group did not significantly lower the risk of death relative to the budesonide-formoterol group, although there was a trend in favor of the 320 µg budesonide triple-therapy group (HR, 0.72; 95% CI, 0.44 to1.16;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				28% reduction; P=0.1721); there was also a trend for the 320 µg budesonide triple-therapy group versus the 160 µg budesonide triple-therapy group (HR, 0.66; 95% CI, 0.41 to1.05; 34% reduction; P=0.0766). The risk of death was also lower (though not significantly) with BGF 160 relative to glycopyrrolate-formoterol group (HR, 0.78; 95% CI, 0.53 to 1.16; 22% reduction; P=0.2244) and was similar for the 160 µg budesonide triple-therapy group relative to the budesonide-formoterol group.
Wedzicha et al.[215] (2008) Fluticasone propionate -salmeterol 500-50 µg BID vs tiotropium 18 µg QD	AC, DB, MC, RCT Patients 40 to 80 years of age with COPD, smoking history, and post-bronchodilator FEV_1 of <50%	N=1,323 2 years	Primary: Exacerbations Secondary: All-cause mortality	Primary: Over 2 years, 62% of the fluticasone propionate -salmeterol group and 59% of the tiotropium group had at least one exacerbation requiring therapeutic intervention. The overall rates of exacerbations were 1.28/year for the fluticasone propionate -salmeterol group and 1.32/year for the tiotropium group, with no difference between rates (P=0.656). Secondary: Mortality was significantly lower among the fluticasone propionate -salmeterol group, 21 (3%), than the tiotropium group, 38 (6%), during the study period (P=0.032). Specifically, cardiac disorders were associated with death in 9 (1%) of fluticasone propionate -salmeterol treated patients and 19 (3%) tiotropium treated patients.
Make et al.[216] (2005) Fluticasone propionate -salmeterol 250-50 µg BID vs ipratropium-albuterol 36-206 µg QID	DB, MC, PG, RCT Patients 40 to 85 years of age with moderate to severe COPD, FEV_1/FVC ratio ≤70%, FEV_1 >0.70 L and ≤70% predicted normal value (or if ≤0.70 L, then ≥40% predicted), smoking history of ≥10 pack years, use of inhaled short acting bronchodilator for	N=361 8 weeks	Primary: Morning pre-dose FEV_1 Secondary: Morning PEF values, 6-hour FEV_1 AUC, percentage of symptom free nights, dyspnea, overall combined daytime symptom score	Primary: Statistically significant improvement in morning pre-dose FEV_1 in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group (P<0.001). Secondary: Statistically significant improvement in mean FEV_1 AUC in fluticasone propionate -salmeterol group at week eight compared to ipratropium-albuterol group (P=0.002). Statistically significant improvement in morning PEF values in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group at week one and throughout study (P<0.001). Mean post-administration FEV_1 values significantly higher in the ipratropium-albuterol group at 0.5, one, and two hours compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	COPD for ≥30 days			fluticasone propionate -salmeterol group (P<0.001), but higher in the fluticasone propionate -salmeterol group at six hours (P=0.003). Dyspnea scores significantly higher in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group (P=0.026), though improvements over baseline observed in both groups. Significantly greater reduction in overall daytime symptom score in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group (change from baseline, -46.7 vs -28.1; P=0.024). Statistically significant increase in albuterol-free nights in fluticasone propionate -salmeterol group compared to ipratropium-albuterol group (change from baseline is 19 vs 7.3%; P<0.001), and a similar increase in albuterol-free days (change from baseline is 34.7 vs 26.7%; P=0.021).
Rabe et al.[217] (2008) Fluticasone propionate 500 µg and salmeterol 50 µg BID vs tiotropium 18 µg QD and formoterol 12µg BID	DB, MC, PG, RCT Patients ≥40 years of age with COPD, smoking history >10 pack-years, and stable airway obstruction	N=605 6 weeks	Primary: FEV_1 area under the curve for the time period 0 to 12 h ($AUC_{0–12}$) and peak FEV_1 Secondary: Not reported	Primary: Lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone propionate (mean difference in FEV_1 $AUC_{0–12}$, 78 mL; P=0.0006; mean difference in FVC $AUC_{0–12}$, 173 mL; P<0.0001). Peak responses were in favor of tiotropium plus formoterol (difference in peak FEV_1, 103 mL; P<0.0001; difference in peak FVC, 214 mL; P<0.0001), as were FEV_1 and FVC at each individual time point after dose (P<0.05). Both treatments were well tolerated. Secondary: Not reported
Saito et al.[218] (2015) Fluticasone propionate and salmeterol 250/50 µg inhaled BID	DB, DD, MC, RCT, XO Japanese patients 40 to 80 years of age with a diagnosis of COPD, >10 pack	N=53 16 weeks Patients spent four weeks in each treatment	Primary: Post-morning dose specific airway conductance (sGAW) $AUC_{0–4h}$ on day 28	Primary: A statically significant improvement in post-morning dose sGAW $AUC_{0–4h}$ on day 28 was seen in the fluticasone propionate/salmeterol plus tiotropium group compared to the two other treatment groups. The ratio of endpoint adjusted mean for the post morning dose sGAW $AUC_{0–4h}$ on day 28 in the fluticasone propionate/salmeterol plus tiotropium group was 1.071 (SE, 0.0263; 97.5% CI, 1.009 to 1.136; P=0.011 compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus tiotropium 18 µg inhaled QD vs fluticasone propionate and salmeterol 250/50 µg inhaled BID vs tiotropium 18 µg inhaled QD	year smoking history, post-bronchodilator FEV_1 30 to 75% of predicted, post bronchodilator FEV_1 to FVC ratio <70%, and mMRC dyspnea score ≥1.	group with two weeks of washout in between	Secondary: Spirometry measures, rescue medication use, and adverse events	tiotropium group and 1.068 (SE, 0.0261; 97.5% CI, 1.007 to 1.133; P=0.013) compared to the fluticasone propionate/salmeterol group. Secondary: On day 28, fluticasone propionate/salmeterol plus tiotropium provided significantly greater improvements in trough FEV_1 and post dose FEV_1 compared to the two other treatment groups. Differences in rescue medication use was not statically significant between treatment groups. Adverse events were reported by 33% of patients in the fluticasone propionate/salmeterol plus tiotropium group, 22% of patients in the fluticasone propionate/salmeterol and 16% of patients in the tiotropium group.
Aaron et al.[219] (2007) Fluticasone propionate - salmeterol 250-25 µg, 2 inhalations BID and tiotropium 18 µg QD vs tiotropium 18 µg QD and salmeterol 25 µg, 2 inhalations BID vs tiotropium 18 µg QD	DB, MC, PC, RCT Patients ≥ 35 years of age with ≥ 1 COPD exacerbation in last 12 months requiring systemic steroids or antibiotics; history of ≥10 pack-years of cigarette smoking; documented chronic airflow obstruction with FEV_1/FVC ratio <0.70 and a postbronchodilator FEV_1 ≤65% of the predicted value	N=449 1 year	Primary: Proportion of patients who experienced an exacerbation of COPD requiring treatment with systemic steroids or antibiotics Secondary: Not reported	Primary: The proportion of patients in the tiotropium group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium+salmeterol group (64.8%; difference, -2.0 percentage points; 95% CI, -12.8 to 8.8). The proportion of patients in the tiotropium group who experienced an exacerbation (62.8%) did not differ from that in the tiotropium+fluticasone propionate -salmeterol group (60.0%; difference, 2.8 percentage points; CI, -8.2 to 13.8). Tiotropium+fluticasone propionate-salmeterol improved lung function (P=0.049) and disease-specific quality of life (P=0.01) and reduced the number of hospitalizations for COPD exacerbation (incidence rate ratio, 0.53; CI, 0.33 to 0.86) and all-cause hospitalizations (incidence rate ratio, 0.67; CI, 0.45 to 0.99) compared with tiotropium. Tiotropium+salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo. NOTE: More than 40% of patients who received tiotropium+placebo and tiotropium+salmeterol discontinued therapy prematurely, and many crossed over to treatment with OL inhaled steroids or LABA. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Vogelmeier et al.[220] (2016) AFFIRM COPD Salmeterol/ fluticasone 50/500 µg BID vs aclidinium/ formoterol 400/12 µg BID	AC, DB, MC, RCT Patients ≥40 years of age with a smoking history ≥10 pack-years, post-bronchodilator FEV_1/FVC <70%, and FEV_1 <80% predicted normal	N=933 24 weeks	Primary: Peak FEV_1 at week 24 Secondary: TDI focal score, TDI and SGRQ responders, exacerbations, use of reliever medication	Primary: Peak FEV_1 was greater with aclidinium/formoterol versus salmeterol/fluticasone at week 24, with significant differences observed after the first dose on day one and at all intervening time-points (all P<0.0001) Secondary: Noninferiority of aclidinium/formoterol versus salmeterol/fluticasone in TDI focal score was demonstrated at week 24 (95% CI, −0.46 to 0.46), as well as at week four (95% CI, −0.34 to 0.40) and week 12 (95% CI, −0.43 to 0.39). At week 24, 55.6% of patients in the aclidinium/formoterol group and 54.5% in the salmeterol/fluticasone group achieved improvements in TDI greater than the minimum clinically important difference (≥1 unit). Mean improvements in SGRQ total scores at week 24 were similar following treatment with aclidinium/formoterol or salmeterol/fluticasone (−4.7 and −5.7, respectively; P=0.27). At week 24, 52.6% of patients in the aclidinium/formoterol group and 55.8% in the salmeterol/fluticasone group achieved improvements from baseline in SGRQ total scores greater than the minimum clinically important difference (≥4 units). There were no significant differences in the incidence of exacerbations between the aclidinium/formoterol and salmeterol/fluticasone groups. There was no significant difference between groups in the use of relief medication (both 0.9 puffs per day at week 24).
Lipson et al.[221] (2017) FULFIL Triple therapy (fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg; ELLIPTA inhaler) once-daily	DB, DD, MC, RCT Patients ≥40 years of age with COPD defined as being in Global Initiative for Chronic Obstructive Lung Disease group D	N=1,810 24 weeks	Primary: Co-primary endpoints were change from baseline in trough FEV_1 and in SGRQ total score at Week 24 Secondary: Proportion of patients with a clinically	Primary: At Week 24, the mean changes from baseline in trough FEV_1 were 142 ml (95% CI, 126 to 158) for triple therapy and −29 ml (95% CI, −46 to −13) for BUD/FOR; the difference between triple therapy and BUD/FOR was 171 mL (95% CI, 148 to 194; P<0.001). Clinically meaningful improvements in SGRQ total score were observed in both treatment groups. The changes from baseline in SGRQ were −6.6 units (95% CI, −7.4 to −5.7) with triple therapy and −4.3 (95% CI, −5.2 to −3.4) with BUD/FOR. The between-treatment difference in improvement in SGRQ total score was −2.2 units (95% CI, −3.5 to −1.0; P<0.001). Secondary: At Week 24, an increase of at least 100 mL from baseline in trough FEV_1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ICS/LABA therapy (budesonide-formoterol 400-12 µg; Turbuhaler) twice-daily			meaningful change from baseline in trough FEV_1 (≥100 ml) and change from baseline SGRQ total score (≥4-unit decrease), proportion of responders	was achieved by a larger proportion of patients in the triple therapy group (50%) than in the BUD/FOR group (21%). The OR of achieving versus not achieving this increase was in favor of triple therapy (OR, 4.03; 95% CI, 3.27 to 4.97; P<0.001). A larger proportion of patients in the triple therapy group (50%) than in the BUD/FOR group (41%) experienced a clinically meaningful improvement from baseline (≥4-unit decrease) in SGRQ total score in the at Week 24. The OR of response versus nonresponse was in favor of triple therapy (OR, 1.41; 95% CI, 1.16 to 1.70; P<0.001).
Bremner et al.[222] (2018) Fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg (triple therapy) once daily vs fluticasone furoate-vilanterol 100-25 µg and umeclidinium 62.5 µg once daily	DB, MC, NI, RCT Patients ≥40 years of age with COPD and ≥1 moderate/severe exacerbation in the 12 months before screening, smoking history ≥10 pack-years, post-bronchodilator FEV_1/FVC <70%	N=1,055 24 weeks	Primary: Change from baseline in trough FEV_1 Secondary: SGRQ and TDI focal score outcomes, adverse events	Primary: The mean change from baseline in trough FEV_1 at Week 24 was 107 mL (95% CI, 87 to 126) for triple therapy and 81 mL (95% CI, 61 to 100) for FF/VI + UMEC; the between-treatment difference was 26 mL (95% CI, -2 to 53). Triple therapy was considered non-inferior to FF/VI + UMEC. Secondary: The proportion of responders based on the SGRQ Total score at Week 24 was similar in the triple therapy group (50%) and FF/VI + UMEC group (51%); the OR of response versus non-response for triple therapy versus FF/VI + UMEC was 0.92 (95% CI, 0.71 to 1.20). The mean change from baseline in SGRQ Total score at Week 24 was − 5.8 (95% CI, -7.0 to − 4.7) for triple therapy and − 4.9 (95% CI, -6.1 to − 3.8) for FF/VI + UMEC; the between-treatment difference was − 0.9 (95% CI, -2.5 to 0.7). The proportion of responders based on TDI focal score at Week 24 was the same for both groups (56% in each group; OR of response versus non-response for triple therapy versus FF/VI + UMEC was 0.95; 95% CI, 0.72 to 1.25). The mean TDI focal score at Week 24 was 2.0 (95% CI, 1.8 to 2.3) for triple therapy and 1.9 (95% CI, 1.6 to 2.1) for FF/VI + UMEC; the between-treatment difference was 0.1 (95% CI, -0.2 to 0.5). The proportion of patients who experienced at least one adverse event was comparable between both treatment groups (48%); the proportion of patients who had at least one serious adverse event was 10% in the triple therapy group and 11% in the FF/VI + UMEC group. The most frequent adverse events were viral upper respiratory tract infection (triple therapy, 11%; FF/VI + UMEC, 10%), headache (6% in each group), and COPD

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(triple therapy, 4%; FF/VI + UMEC, 6%).
Lipson et al.[223] (2018) IMPACT Fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg (triple therapy) once daily vs fluticasone furoate-vilanterol 100-25 µg once daily vs umeclidinium-vilanterol 62.5-25 µg once daily	DB, MC, PG, RCT Patients ≥40 years of age with symptomatic COPD, post-bronchodilator FEV_1 ≤50% of predicted and a history of at least one moderate or severe exacerbation in the previous year, or an FEV_1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year	N=10,355 52 weeks	Primary: Annual rate of moderate or severe COPD exacerbations Secondary: Trough FEV_1, SGRQ score	Primary: The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% CI, 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). Secondary: For the spirometric outcome of the mean change from baseline in trough FEV_1, the difference between the triple-therapy and fluticasone furoate–vilanterol groups was 97 ml (95% CI, 85 to 109; P<0.001), and the difference between the triple-therapy and umeclidinium–vilanterol groups was 54 ml (95% CI, 39 to 69; P<0.001). There were significant differences between the triple-therapy group and the fluticasone furoate–vilanterol and umeclidinium–vilanterol groups in the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least four points (P<0.001 for both comparisons on both outcomes).
Bansal et al.[224] (2021) Fluticasone furoate-umeclidinium-vilanterol 100-62.5-25 µg once daily vs tiotropium 18 µg	DB, MC, PG, RCT Patients ≥40 years of age, current or former smoker with a history of ≥10 pack-years, had an established clinical history of COPD, had been receiving daily COPD maintenance treatment with	N=800 12 weeks	Primary: Change from baseline in trough FEV_1 at day 85 Secondary: Change from baseline in trough FEV_1 at days 28 and 84, change from baseline in SGRQ total score at Days 28 and 84,	Primary: The mean change from baseline in trough FEV_1 at Day 85 was significantly greater with fluticasone furoate-umeclidinium-vilanterol versus tiotropium, with a treatment difference of 95 mL (95% CI, 62 to 128; P<0.001). Secondary: The mean change from baseline in trough FEV_1 was significantly greater with fluticasone furoate-umeclidinium-vilanterol versus tiotropium at both Day 28 and Day 84, with treatment differences of 122 mL (95% CI, 94 to 150; P<0.001) and 87 mL (94% CI, 56 to 118; P<0.001), respectively. A significantly greater mean decrease from baseline in SGRQ total score

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily	tiotropium alone for ≥3 months, had a post-bronchodilator foFEV1 of <50% predicted score ≥10.		proportion of SGRQ total score responders at Days 28 and 84, change from baseline in CAT score at Days 28 and 84, proportion of CAT score responders at Days 28 and 84 and moderate or severe exacerbation events	was observed with fluticasone furoate-umeclidinium-vilanterol versus tiotropium at both Day 28 and Day 84. The between treatment differences were -3.0 (95% CI, -4.7 to -1.3; P<0.001) and -3.2 (95% CI, -5.0 to -1.4; P<0.001), respectively. The odds of being a SGRQ total score responder were significantly greater with fluticasone furoate-umeclidinium-vilanterol versus tiotropium at Day 28 (OR, 1.61; 95% CI, 1.20 to 2.15; P=0.001) and Day 84 (OR, 1.62; 95% CI, 1.22 to 2.17; P=0.001). CAT score decreased significantly from baseline with fluticasone furoate-umeclidinium-vilanterol versus tiotropium at Days 28 and 84. Between treatment differences were -0.9 (95% CI, -1.5 to -0.2; P=0.006) and -1.2 (95% CI, -1.9 to -0.5; P=0.001), respectively. In total, 27 (7%) and 43 (11%) patients receiving fluticasone furoate-umeclidinium-vilanterol and tiotropium, respectively, experienced a moderate/severe exacerbation during the 12-week study period. Severe exacerbations were seen in 5 (1%) and 3 (<1%) patients receiving fluticasone furoate-umeclidinium-vilanterol and tiotropium, respectively.
Lee et al.[225] (2008) Exposure to ICSs, ipratropium, LABAs, theophylline and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however, this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.

Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QID=four times daily, QPM=every evening
Study abbreviations: AC=active control, ANOVA=analysis of variance, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, XO=cross over
Miscellaneous abbreviations: ACT=asthma control test, AE= Adverse event, AMP PC_{20}=provocation dose of AMP to decrease forced vital capacity by 20%, AQLQ=asthma quality of life questionnaire, C-ACT= Childhood Asthma Control Test, CAT= COPD Assessment Tests, CFC=chlorofluorocarbon, CVD= cardiovascular disease, DPI=dry-powder inhaler, EBC= exhaled breath condensate, eNO=exhaled nitric oxide, $FEF_{25\ to\ 75\%}$=forced expiratory flow at 25 to 75% of FVC, FeNO= fractional exhaled nitric oxide, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, IR= Incidence Ratio, LABA=long-acting β_2-agonist, LS= least squares, MDI=metered-dose inhaler, MDPI= multidose dry powder inhaler, mMRC= modified Medical Research Council, NO=nitrous oxide, NRQLQ=Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire, OR=odds ratio, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQS=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PK= Pharmacokinetics, PPB=parts per billion, SABA=short acting β_2-agonist, SE= standard error, sGaw= specific airway conductance, SGRQ-C =St George's Respiratory Questionnaire-COPD, SF-36=Short-Form-36, WMD=weighted mean difference, wmFEV= weighted mean FEV_1

IX. Additional Evidence

Dose Simplification

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. Evidence-based guidelines for the selection of the appropriate inhalation delivery device have been published. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[226] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[226] It has been estimated that up to 70% of patients using metered dose inhalers fail to use them correctly.[226] Incorrect technique can result in decreased drug delivery and potentially decreased efficacy. The ability of a patient to use a particular inhalation device correctly may be affected by a number of factors. These factors include age, cognitive status, coordination, manual dexterity/strength, severity of respiratory disease, and visual acuity.[227] Adherence to inhaled therapy is often poor, with rates of 40 to 72% being reported.[228] Patient preference should be considered when selecting an inhalation delivery device.[227] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.[227]

Dorais et al. analyzed pharmacy claims to assess adherence with leukotriene modifiers and inhaled corticosteroids.[229] Compared to patients receiving inhaled corticosteroids, patients receiving a leukotriene modifier were more likely to refill their prescriptions at least once during the first year of treatment (67.9 vs 52.7%), were less likely to discontinue treatment (relative risk, 0.46; 95% confidence interval, 0.85 to 0.98), and were more likely to be on treatment longer during the first year of therapy (38 vs 19%; all, $P<0.001$). Stoloff et al. evaluated refill persistence with fluticasone propionate -salmeterol, fluticasone propionate plus salmeterol in separate inhalers, fluticasone propionate plus montelukast, fluticasone propionate monotherapy, and montelukast monotherapy.[230] Patients in the fluticasone propionate -salmeterol group had significantly more refills compared to patients receiving other fluticasone propionate preparations, and had similar refill rates as patients in the montelukast group. In a similar study, Stempel et al. reported the same findings with regards to refill persistence.[231] In addition, the mean number of short-acting bronchodilator prescriptions was significantly lower in patients receiving fluticasone propionate -salmeterol compared to those receiving montelukast monotherapy ($P<0.0001$). Sovani et al. evaluated adherence rates with budesonide/formoterol compared to budesonide plus a short-acting β_2-agonist.[232] Adherence with budesonide was found to be approximately 60% of the prescribed dose. Patients receiving budesonide/formoterol used approximately 80% more budesonide than participants in the control group ($P<0.001$). Sherman et al. assessed adherence rates in children with persistent asthma who were Medicaid recipients.[233] Adherence was 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn. Murphy et al. evaluated the differences in caregiver satisfaction and adherence to therapy with budesonide inhalation suspension administered once-daily and cromolyn sodium inhalation solution administered four-times-daily.[234] Adherence rates were 76% in the budesonide group compared to 57% in the cromolyn group. Additionally, 54.6% of caregivers rated budesonide as “highly or very convenient” compared with only 23% for cromolyn. While 77% of caregivers found the budesonide formulation easy to administer, only 47% reported ease of use with the cromolyn inhalation. The results of the survey indicated significantly higher parental satisfaction and improved compliance with budesonide compared to cromolyn due to ease of use and convenience of once-daily administration ($P\leq0.001$).

Stable Therapy

A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits

Sheikh et al. evaluated health care resource utilization in patients receiving flunisolide and fluticasone propionate.[35] There was a significant improvement in emergency room visits with fluticasone propionate compared to flunisolide ($P=0.004$). Mean hospital admissions for asthma were also lower in the fluticasone propionate group compared to the flunisolide group ($P<0.002$). A retrospective study of approximately 17,000 patients demonstrated that inhaled corticosteroids significantly reduced emergency department visits and hospitalizations due to asthma.[235]

X. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Respiratory Agents-Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Beclomethasone	aerosol inhaler	QVAR®	$$$$$	N/A
Budesonide	dry powder inhaler, inhalation suspension	Pulmicort ®*	$$$$$	$$$$$
Ciclesonide	aerosol inhaler	Alvesco®	$$$$$	N/A
Fluticasone furoate	dry powder inhaler	Arnuity Ellipta®	$$$$$	N/A
Fluticasone	aerosol inhaler, dry powder inhaler	ArmonAir Digihaler®, Flovent Diskus®, Flovent HFA®*	$$$$$	N/A
Mometasone	dry powder inhaler	Asmanex®	$$$$$	N/A
Combination Products				
Budesonide and formoterol	aerosol inhaler	Symbicort®*	$$$$$	$$$$$
Budesonide, glycopyrrolate and formoterol	Aerosol inhaler	Breztri®	$$$$$	N/A
Fluticasone and salmeterol	aerosol inhaler, dry powder inhaler	Advair Diskus®*, Advair HFA®, Airduo Digihaler®, Airduo Respiclick®*	$$$$$	$$$$
Fluticasone and vilanterol	dry powder inhaler	Breo Ellipta®*	$$$$$	N/A
Fluticasone, umeclidinium, and vilanterol	dry powder inhaler	Trelegy Ellipta®	$$$$$	N/A
Mometasone and formoterol	aerosol inhaler	Dulera®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

XI. Conclusions

The respiratory agents-corticosteroids (inhaled corticosteroids) are approved for the treatment of asthma and chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[1-21] They are available as single entity products, as well as in combination with a long-acting β_2- agonist (formoterol, salmeterol, or vilanterol). Budesonide inhalation solution and two formulations of the fluticasone propionate-salmeterol dry powder inhaler are currently available in a generic formulation. The combination product fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta®) was approved in 2017 for the maintenance treatment of patients with COPD. It is the first once-daily single inhaler triple therapy for the treatment of patients with COPD in the US.[14] In 2020, budesonide, glycopyrrolate, and formoterol fumarate combination product (Breztri®), dosed twice daily, was approved for the maintenance treatment of patients with COPD.[19] Two products with built-in electronic modules which detect, record, and store data on inhaler events for transmission to a mobile app, fluticasone propionate (ArmonAir Digihaler®) and fluticasone propionate and salmeterol (Airduo Digihaler®) were approved in 2020 and 2019, respectively.[20,21]

The inhaled corticosteroids are the most effective long-term medications for the treatment of mild, moderate, or severe persistent asthma; therefore, they are consistently recommended as first-line therapy.[26,27] Guidelines do not give preference to one inhaled corticosteroid over another for the treatment of asthma. Most of the benefit is achieved using relatively low doses, and increasing the dose provides little additional benefit.[26] However, due to variability in individual responses and poor adherence, some patients may need higher doses to achieve adequate control of their asthma symptoms.[26] Higher doses may also be needed in patients who smoke. The 2021 Global Initiative for Asthma (GINA) includes recommendations published in 2019, prompted by concerns about the risks and consequences of the long-standing approach of initiating asthma treatment with short-acting β_2-agonists (SABA) alone. "For safety, GINA no longer recommends treatment of asthma in adolescents and adults with SABA alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment."[26] For the controller management of asthma, low-dose ICS is recommended.[26] When additional therapy is needed, guidelines recommend the use of a medium dose ICS and then adding on long-acting antimuscarinic agent (LAMA) for adults and adolescents over 12 years of age. For children six to 11 years of age, guidelines recommend use of ICS-long-acting β_2-agonist (LABA) combination when additional therapy is needed.[26] The boxed warnings have been removed from the combination products in this class, and warnings were added for serious asthma-related events. The warning states that use of long-acting β_2-agonists (LABAs) as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABAs are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.[1,2]

Numerous trials have been conducted with the inhaled corticosteroids. They have been shown to improve pulmonary function, prevent symptoms and exacerbations, reduce the need for emergency department treatment, and reduce asthma mortality compared to other maintenance therapies (e.g., leukotriene modifiers, long-acting β_2-agonists, cromolyn, or theophylline). When administered at equipotent doses via comparable delivery devices, the inhaled corticosteroids do not appear to differ in their ability to control asthma symptoms, prevent exacerbations, or reduce the need for rescue medication use. When comparing combination therapy to monotherapy, the more aggressive treatment regimens improved asthma outcomes to a greater extent than the less-intensive treatment regimens. Several studies have demonstrated similar outcomes with the fixed-dose combination inhalers compared to the coadministration of their individual components as separate inhalers. Studies directly comparing the fixed-dose combination products (budesonide-formoterol vs fluticasone propionate -salmeterol) have shown conflicting results with regards to asthma outcomes.[28-225]

Most studies have indicated that the existing medications to treat COPD do not modify the long-term decline in lung function.[23] Therefore, the goal of treatment is to decrease symptoms and complications. Bronchodilators are central to the symptomatic management of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline was updated in 2022. Initiation of maintenance pharmacological therapy should be based on the individualized assessment of symptoms and exacerbation risk. Generally, a LABA or long-acting antimuscarinic agent (LAMA) is recommended when beginning treatment. Patients may be started on single long-

acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. Short-acting inhaled β_2-agonists with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation.[23]

Specific inhalation techniques are necessary for the proper use of each of the available types of inhaler devices. According to the American College of Chest Physicians (ACCP)/American College of Asthma, Allergy, and Immunology (ACAAI) guidelines, devices used for the delivery of bronchodilators and steroids are equally effective; therefore, efficacy should not be the basis for selecting one device over another.[226] However, it should be noted that devices studied are only equally effective in patients who can use them appropriately.[226] When selecting an inhalation delivery device for patients with asthma and COPD, health care providers should consider the following: device/drug availability, clinical setting, patient age and the ability to use the selected device correctly, device use with multiple medications, drug administration time, convenience in both outpatient and inpatient settings, as well as physician and patient preference.[226]

Given the role of the single entity inhaled corticosteroids in the management of asthma, one or more brand products within the class reviewed offers significant clinical advantage in general use over the generic products (if applicable), but is comparable to all other brands in the same class. All brand fixed-dose combination inhaled corticosteroids within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The brand fixed-dose combination inhaled corticosteroids should be available through the medical justification portion of the prior authorization process for patients who require the combination of an inhaled corticosteroid and LABA to control their respiratory symptoms.

XII. Recommendations

Alabama Medicaid should work with manufacturers on cost proposals so that at least one single entity brand respiratory agents-corticosteroids is selected as a preferred agent.

No brand fixed-dose combination respiratory agents-corticosteroid is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XIII. References

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August 10, 2022

I. Overview

The respiratory smooth muscle relaxants (xanthines) are approved for the treatment of asthma, chronic bronchitis, and emphysema. Their respiratory effects are thought to be mediated through competitive inhibition of phosphodiesterase with a resultant increase in cyclic adenosine monophosphate (AMP). This produces relaxation of bronchial smooth muscle (bronchodilation) and suppresses the response of the airway to stimuli.[1-3]

Theophylline is the reference xanthine derivative from which aminophylline was developed. Aminophylline is a 2:1 complex of theophylline and ethylenediamine.[1,2] Xanthines are often carefully titrated according to weight-based dosing due to their narrow therapeutic index. For bronchodilatory effects, therapeutic serum levels of theophylline should fall between 10 to 20 µg/mL. The xanthines generally share similar side effect profiles, precautions, and contraindications.[1,2]

The respiratory smooth muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All agents are available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Respiratory Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aminophylline	injection	N/A	aminophylline
Theophylline	elixir*, extended-release capsule, extended-release tablet*, injection*, oral solution*	Theo-24®	theophylline

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the respiratory smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Respiratory Smooth Muscle Relaxants

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022)**[13]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, sputum production, history of recurrent lower respiratory tract infections and/or a history of exposure to risk factors for the disease. • Spirometry is required to make the diagnosis; the presence of a post-bronchodilator Forced Expiratory Volume in one second (FEV_1)/ Forced Vital Capacity (FVC) ratio of <0.07 confirms the presence of persistent airflow limitation. • The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbation, hospital admissions, or death), in order to guide therapy. • Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer; these comorbidities should be actively sought and treated appropriately when present as they can influence

Clinical Guidelines	Recommendations
	mortality and hospitalizations independently. Prevention and maintenance therapy • Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates. • The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present. • Pharmacological therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbation, and improve health status and exercise tolerance. • Each pharmacological treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference, and ability to use various drug delivery devices. • Inhaler technique needs to be assessed regularly. • COVID-19 vaccines are highly effective against SARS-CoV-2 infection and people with COPD should have the COVID-19 vaccination in line with national recommendations. • Influenza vaccination decreases lower respiratory tract infections. • Pneumococcal vaccination decreases lower respiratory tract infections. • CDC recommends the Tdap vaccination (dTaP/dTPa) in COPD patients to protect against pertussis, tetanus and diphtheria, in those who were not vaccinated in adolescence and Zoster vaccine to protect against shingles for adults with COPD aged ≥50 years. • Pulmonary rehabilitation improves exercise capacity, symptoms and quality of life across all grades of COPD severity. • In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival. • In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. Individual patient factors must be considered when evaluating the patient's need for supplemental oxygen. • In patients with severe chronic hypercapnia and a history of hospitalizations for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization. • In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial. • Palliative approached are effective in controlling symptoms in advanced COPD. Pharmacologic therapy for stable COPD • Bronchodilators ○ Inhaled bronchodilators in COPD are central to symptom management and are commonly given on a regular basis to prevent or reduce symptoms. ○ Regular and as-needed use of short-acting β_2-agonist (SABA) or short-acting antimuscarinic (SAMA) improves FEV_1 and symptoms. ○ Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms. ○ Long-acting β_2.agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) improve lung function, dyspnea, health status, and reduce exacerbation rates. ○ LAMAs have a greater effect on reducing exacerbations than LABAs and decrease hospitalizations. ○ Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy. ○ Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy.

Clinical Guidelines	Recommendations
	○ Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance. ○ Theophylline exerts a small bronchodilator effect in stable COPD and that is associated with modest symptomatic benefits. • Anti-inflammatory therapy ○ Inhaled corticosteroids ▪ An inhaled corticosteroid (ICS) combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. ▪ Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease. ▪ Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations. ○ Oral glucocorticoids ▪ Long-term use of oral glucocorticoids has numerous side effects with no evidence of benefits. ○ Phosphodiesterase-4 (PDE4) inhibitors ▪ In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations, a PDE4 inhibitor improves lung function and reduces moderate to severe exacerbations and improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations. ○ Antibiotics ▪ Long-term azithromycin and erythromycin therapy reduces exacerbations over one year. ▪ Treatment with azithromycin is associated with an increased incidence of bacterial resistance and hearing test impairments. ○ Mucoregulators and antioxidant agents ▪ Regular treatment with mucolytics such as erdosteine, carbocysteine, and N-acetylcysteine (NAC) reduces the risk of exacerbations in select populations. ○ Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy. ○ Leukotriene modifiers have not been adequately tested in COPD patients. ○ Intravenous augmentation therapy may slow down the progression of emphysema. ○ There is no conclusive evidence of a beneficial role of antitussives in patients with COPD. Vasodilators do not improve outcomes and may worsen oxygenation. <u>Management of stable COPD</u> • LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy. • Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator should be escalated to two. • Inhaled bronchodilators are recommended over oral bronchodilators. • Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable. • Long-term monotherapy with ICS is not recommended.

Clinical Guidelines	Recommendations
	• Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators. • Long-term therapy with oral corticosteroids is not recommended. • In patients with severe to very severe airflow limitation, chronic bronchitis, and exacerbations the addition of a PDE4 inhibitor to a treatment with long-acting bronchodilators with/without ICS can be considered. • Preferentially but not only in former smokers with exacerbations despite appropriate therapy, macrolides (in particular azithromycin) can be considered. • Statin therapy is not recommended for prevention of exacerbations. • Antioxidant mucolytics are recommended only in select patients. • Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. • Antitussives cannot be recommended. • Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD. • Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease. Management of exacerbations • The most common causes of an exacerbation are viral respiratory tract infections. • The goal of treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events. • SABA with or without short-acting anticholinergics are recommended as the initial bronchodilators for treatment of an acute exacerbation. • Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge. • Systemic corticosteroids can improve lung function (FEV_1), oxygenation, and shorten recovery time and length of hospital stay. Duration of therapy should not be more than five to seven days. • Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be five to seven days. • Methylxanthines are not recommended due to increased side effect profiles.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and**	Diagnosis • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-

Clinical Guidelines	Recommendations
European Respiratory Society (2011)[5]	agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).
Department of Veterans Affairs/ Department of Defense: **Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2021)**[15]	Diagnosis and classification • Post-bronchodilator spirometry is suggested to confirm clinical diagnosis of COPD. • There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD. Risk reduction and first-line therapy • Smoking cessation is recommended for prevention and risk reduction of COPD. • Routine vaccination for influenza and pneumococcal pneumonia is suggested for prevention and risk reduction of COPD exacerbations. • LAMA is recommended as first-line therapy in patients with symptomatic COPD. • Inhaled LABA should not be offered as first-line therapy in patients with symptomatic COPD, unless a LAMA is not tolerated or is contraindicated. • ICS should not be offered to patients with symptomatic COPD as a first-line therapy. • For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a LAMA, adding a LABA to LAMA therapy is suggested. • If choosing dual therapy, offering LABA with ICS for patients with COPD is not recommended. • In patients with COPD who are on combination therapy with a LAMA/LABA and continue to have COPD exacerbations, adding an ICS as a third medication is suggested. • There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy. • Consider withdrawal of ICS in patients with COPD without moderate to severe exacerbations in the last two years. • There is insufficient evidence to recommend for or against the use of NAC preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough). • There is insufficient evidence to recommend for or against the use of antibiotics

Clinical Guidelines	Recommendations
	for outpatient COPD exacerbations (C-reactive protein guided or not). • Providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia or chronic stable resting moderate hypoxemia with signs of tissue hypoxia is recommended. • Routinely offering ambulatory long-term supplemental oxygen is not suggested for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen. • In patients with COPD, starting or continuing cardio-selective beta-blockers is suggested only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction). • Supported self-management program and telehealth support should be offered.

Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2021)**[16]	<u>General principles of asthma management</u>
	• The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side effects of treatment. The patient's own goals regarding their asthma and its treatment should also be identified.
	• Effective asthma management requires a partnership between the patient/caregiver and their healthcare providers.
	• Teaching communication skills to healthcare providers and taking into account the patient's health literacy may lead to increased patient satisfaction, better health outcomes, and reduced use of healthcare resources.
	• Asthma treatment is adjusted in a continuous cycle of assessment, treatment, and review of the patient's response in both symptom control and future risk of exacerbations and side effects, and of patient preferences.
	• For population-level decisions about asthma treatment, the 'preferred option' represents the best treatment for most patients, based on evidence from randomized controlled trials, meta-analyses, and observational studies about safety, efficacy and effectiveness, with a particular emphasis on symptom burden and exacerbation risk.
	• For individual patients, treatment decisions should also take into account any patient characteristics or phenotype that predict the patient's likely response to treatment, together with the patient's preferences and practical issues.
	
	<u>Medications and strategies for symptom control and risk reduction</u>
	• For safety, this guideline no longer recommends treatment of asthma in adults and adolescents with SABA alone.
	• This guideline recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, either as-needed (in mild asthma) or daily, to reduce their risk of serious exacerbations and to control symptoms.
	• Choice of reliever
	  ○ Low dose ICS-formoterol is the preferred approach recommended by this guideline.
	  ○ SABA is an alternative if low dose ICS-formoterol is not possible or is not preferred by a patient with no exacerbations on their current therapy.
	• Mild asthma
	  ○ Treatment with regular daily low dose ICS, with as-needed SABA, is highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
	  ○ In adults and adolescents with mild asthma, treatment with as-needed low dose ICS-formoterol reduces the risk of severe exacerbations by about two-thirds compared with SABA-only treatment, and is non-inferior to daily low dose ICS for severe exacerbations, with no clinically important difference in symptom control.
	• Stepping up if asthma remains uncontrolled despite good adherence and inhaler

Clinical Guidelines	Recommendations
	technique ○ Before considering any step up, first check for common problems such as inhaler technique, adherence, persistent allergen exposure, and comorbidities. ▪ For adults and adolescents, the preferred step-up treatment is combination low dose ICS-formoterol as maintenance and reliever therapy. If needed, the maintenance dose of ICS-formoterol can be increased to medium. ▪ Maintenance and reliever therapy is also a preferred treatment option for children six to 11 years of age. ▪ Other step 3 options for adults, adolescents and children include maintenance ICS-LABA plus as-needed SABA or for children six to 11 years, medium dose ICS plus as-needed SABA. ▪ For children, try other controller options at the same step before stepping up. ▪ ICS-formoterol should not be used as the reliever for patients taking a different ICS-LABA maintenance treatment, since clinical evidence for safety and efficacy is lacking. • Stepping down to find the minimum effective dose ○ Consider step down once good asthma control has been achieved and maintained for about three months, to find the patient's lowest treatment that controls both symptoms and exacerbations. ▪ Provide the patient with a written asthma action plan, monitor closely, and schedule a follow-up visit. ▪ Do not completely withdraw ICS unless this is needed temporarily to confirm the diagnosis of asthma. • For all patients with asthma ○ Provide inhaler skills training: this is essential for medications to be effective, but technique is often incorrect. ○ Encourage adherence with controller medication, even when symptoms are infrequent. ○ Provide training in asthma self-management to control symptoms and minimize the risk of exacerbations. ○ For patients with one or more risk factors for exacerbations: ▪ Prescribed regular daily ICS-containing medication, provide a written asthma action plan, and arrange review more frequently than for low-risk patients. ▪ Identify and address modifiable risk factors (e.g., smoking, low lung function). ▪ Consider non-pharmacological strategies and interventions to assist with symptoms control and risk reduction (e.g., smoking cessation, breathing exercises, avoidance strategies). • Difficult-to-treat and severe asthma ○ Patients with poor symptom control and/or exacerbations despite medium or high dose ICS-LABA treatment should be assessed for contributing factors, and asthma treatment optimized. If the problems continue, refer to a specialist center for phenotypic assessment and consideration of add-on therapy including biologics. <u>Categories of asthma medications</u> • *Controller medications*: these medications contain ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. In patients with mild asthma, controller treatment may be delivered through as-needed low dose ICS-formoterol, taken when symptoms occur and before exercise. • *Reliever (rescue) medications*: these are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. They are also recommended for short-term prevention of exercise-

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<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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induced bronchoconstriction. Relievers include as-needed low dose ICS-formoterol, or as-needed SABA. Reducing and, ideally, eliminating the need for reliever treatment is both an important goal in asthma management and a measure of the success of asthma treatment.
• Add-on therapies for patients with severe asthma: these may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors.

<u>Initial controller treatment</u>
• For best outcomes, ICS-containing controller treatment should be initiated as soon as possible after the diagnosis of asthma is made.

<u>Personalized approach for adjusting asthma treatment in adults, adolescents, and children six to 11 years of age</u>
• Once treatment has been commenced (see tables below), ongoing treatment decisions are based on a personalized cycle of assessment, adjustment of treatment, and review of the response. Controller medication is adjusted up or down in a stepwise approach. Once good asthma control has been maintained for two to three months, treatment may be stepped down in order to find the patient's minimum effective treatment.
• If a patient has persisting symptoms and/or exacerbations despite two to three months of controller treatment, assess and correct for the following common problems before considering any step up in treatment:
  ○ Incorrect inhaler technique.
  ○ Poor adherence.
  ○ Persistent exposure at home/work to agents such as allergens, tobacco smoke, indoor or outdoor air pollution, or to medications such as β-blockers or (in some patients) non-steroidal anti-inflammatory drugs (NSAIDs).
  ○ Comorbidities that may contribute to respiratory symptoms and poor quality of life.
  ○ Incorrect diagnosis.

<table>
<tr><th colspan="6">Personalized management to control symptoms and minimize future risk (adults and adolescents 12+ years)</th></tr>
<tr><td rowspan="2">Controller and preferred reliever (Track 1)</td><td colspan="2">Steps 1 to 2
As-needed low dose ICS-formoterol</td><td>Step 3
Low dose maintenance ICS-formoterol</td><td>Step 4
Medium dose maintenance ICS-formoterol</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-formoterol</td></tr>
<tr><td colspan="5">Reliever: as-needed low-dose ICS-formoterol</td></tr>
<tr><td rowspan="2">Controller and alternative reliever (Track 2)</td><td>Step 1
Take ICS whenever SABA taken</td><td>Step 2
Low dose maintenance ICS</td><td>Step 3
Low dose maintenance ICS-LABA</td><td>Step 4
Medium/high dose maintenance ICS-LABA</td><td>Step 5
Add-on LAMA
Refer for phenotypic assessment ±anti-IgE, anti-IL5/5R, anti-IL4R
Consider high dose ICS-LABA</td></tr>
<tr><td colspan="5">Reliever: as-needed SABA</td></tr>
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• Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS
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Clinical Guidelines

Recommendations

Personalized management to control symptoms and minimize future risk (six to 11 years of age)

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	Low dose ICS taken when SABA is taken	Daily low dose ICS	Low dose ICS-LABA or medium dose ICS or very low dose ICS-formoterol maintenance and reliever therapy	Medium dose ICS-LABA or low dose ICS-formoterol maintenance and reliever therapy Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on treatment (e.g., anti-IgE)
Other controller options	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA) or low dose ICS taken when SABA taken	Low dose ICS+LTRA	Add tiotropium, or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side effects
Reliever	As-needed SABA (or low dose ICS-formoterol reliever for maintenance and reliever therapy)				

Management of worsening asthma and exacerbations

- Exacerbations represent an acute or sub-acute worsening in symptoms and lung function from the patient's usual status, or in some cases, the initial presentation of asthma.
- Patients who are at an increased risk of asthma-related death should be identified and flagged for more frequent review.
- All patients should be provided with a written asthma action plan appropriate for their level of asthma control and heath literacy, so they know how to recognize and respond to worsening asthma.
  - The action plan should include when and how to change reliever and controller medications, use OCS, and access medical care if symptoms fail to respond to treatment.
  - Patients who deteriorate quickly should be advised to go to an acute care facility or see their doctor immediately.
  - The action plan can be based on changes in symptoms or (in adults) peak expiratory flow.
- For patients presenting with an exacerbation to a primary care or acute care facility:
  - Assessment of exacerbation severity should be based on the degree of dyspnea, respiratory rate, pulse rate, oxygen saturation, and lung function, while starting SABA and oxygen therapy.
  - Immediate transfer should be arranged to an acute care facility if there are signs of severe exacerbation, or to intensive care if the patient is drowsy, confused, or has a silent chest. While transferring the patient, SABA and ipratropium bromide, controlled oxygen, and systemic corticosteroids should be given.
  - Treatment should be started with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer), early introduction of OCS, and controlled flow oxygen if available. Response should be reviewed after one hour.
  - Ipratropium bromide treatment is recommended only for severe exacerbations.
  - Intravenous magnesium sulfate should be considered for patients with severe exacerbations not responding to initial treatment.
  - Chest X-ray or prescribing antibiotics is not routinely recommended.
  - Decisions about hospitalization should be based on clinical status, lung function, response to treatment, recent and past history of exacerbations, and ability to manage at home.
  - Before the patient goes home, ongoing treatment should be arranged. This should include starting ICS-containing controller treatment or stepping up the

Clinical Guidelines	Recommendations

dose of existing controller treatment for two to four weeks and reducing reliever medication to as-needed use.

- Arrange early follow-up after any exacerbation, regardless of where it was managed.
  - Review the patient's symptom control and risk factors for further exacerbations.
  - Prescribe ICS-containing controller therapy to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for two to four weeks.
  - Provide a written asthma action plan and advice about avoiding exacerbation triggers.
  - Check inhaler technique and adherence.

Children five years and younger: assessment and management

- The goals of asthma management in young children are similar to those in older patients:
  - To achieve good control of symptoms and maintain normal activity levels.
  - To minimize the risk of asthma flare-ups, impaired lung development, and medication side effects.
- Wheezing episodes in young children should be treated initially with inhaled SABAs, regardless of whether the diagnosis of asthma has been made. However, for initial episodes of wheeze in children <1 year in the setting of infectious bronchiolitis, SABAs are generally ineffective.
- A trial of controller therapy should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe.
- Response to treatment should be reviewed before deciding whether to continue it. If no response is observed, consider alternative diagnosis.
- The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with a face mask for <3 years of age and mouthpiece for most three to five year olds.
- Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children.

Personalized management of asthma in children 5 years and younger				
	Step 1	**Step 2**	**Step 3**	**Step 4**
Preferred controller choice		Daily low dose ICS	Double 'low dose' ICS	Continue controller & refer to specialist
Other controller options		Daily leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, ↑ ICS frequency, or add intermittent ICS
Reliever	As-needed SABA (all children)			

Consider this step for children with:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern consistent with asthma and asthma symptoms not well-controlled or ≥3 exacerbations per year	Asthma diagnosis, and not well-controlled on low dose ICS	Not controlled on double ICS
		Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months	First check diagnosis, inhaler skills, adherence, exposures	

Management of worsening asthma and exacerbations in children five and younger

- Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise

Clinical Guidelines	Recommendations
	tolerance, impaired daily activities including feeding, and a poor response to reliever medication. • Give a written asthma action plan to parents of young children with asthma so they can recognize a severe attack, start treatment, and identify when urgent hospital treatment is required. o Initial treatment at home is with inhaled SABA, with review after one hour or earlier. o Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in children less than one year of age. o Medical attention should be sought on the same day if inhaled SABA is needed more often that 3-hourly or for more than 24 hours. o There is no compelling evidence to support parent-initiated oral corticosteroids. • In children presenting to primary care or an acute care facility with an asthma exacerbation: o Assess severity of the exacerbation while initiating treatment with SABA (two to six puffs every 20 minutes for first hour) and oxygen (to maintain saturation 94 to 98%). o Recommend immediate transfer to hospital if there is no response to inhaled SABA within one to two hours; if the child is unable to speak or drink, has a respiratory rate >40/minute or has cyanosis; if resources are lacking in the home; or if oxygen saturation is <92% on room air. o Consider oral prednisone/prednisolone 1 to 2 mg/kg/day for up to five days for children attending an emergency department or admitted to hospital, up to a maximum of 20 mg/day for 0 to 2 years, and 30 mg/day for 3 to 5 years; or dexamethasone 0.6 mg/kg/day for two days. If there is a failure of resolution, or relapse of symptoms with dexamethasone, consideration should be given to switching to prednisolone. • Children who have experienced an asthma exacerbation are at risk of further exacerbations. Follow up should be arranged within one to two days of an exacerbation and again one to two months later to plan ongoing asthma management.
British Thoracic Society/ Scottish Intercollegiate Guidelines Network: **British Guideline on the Management of Asthma (2019)[8]**	<u>Pharmacological management</u> • The aim of asthma management is control of the disease. Complete control is defined as no daytime symptoms, no night-time awakening due to asthma, no need for rescue medication, no exacerbations, no limitations on activity including exercise, normal lung function, and minimal side effects from medication. • Lung function measurements cannot be reliably used to guide asthma management in children under five years of age. • Before initiating a new pharmacologic therapy assess adherence with existing therapies, inhaler technique, and eliminate trigger factors. • Reductions in therapy should be considered every three months. If reduction is clinically appropriate, it should be done by decreasing the dose approximately 25 to 50%. • Intermittent reliever therapy: o For all patients, prescribe an inhaled SABA as short term reliever therapy for all patients with symptomatic asthma. o For patients with infrequent, short-lived wheeze, intermittent inhaled SABA may be the only therapy required. o Patients requiring more than one SABA inhaler a month should be assessed and considered for regular preventer therapy. • Introduction of regular preventer therapy: o ICS are the recommended preventer drug for adults and children for achieving overall treatment goals. There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe

Clinical Guidelines	Recommendations
	and effective in children under five years of age with asthma. o ICS should be considered for patients with any of the following asthma-related features: asthma attack in the last two years; using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, ICS should be considered in adults and children aged five to 12 years of age who have had an asthma attack requiring oral corticosteroids in the last two years. o ICS typical starting dose is low dose for adults and very low dose for children. Titrate the dose to the lowest dose at which effective control of asthma is maintained. o ICS should initially be administered twice daily, except ciclesonide which is administered once daily. o Once a day ICS at the same total daily dose can be considered if good control is established. o Health care providers should be aware that higher doses of ICS may be needed in smokers or ex-smokers. • Initial add-on therapy: o In adults, the first choice add-on therapy to an ICS is a LABA, which should be considered before increasing the dose of the ICS. o In children ≥ five years, a LABA or LTRA can be considered as initial add on therapy. o LABAs should only be started in patients who are already on ICS, and the ICS should be continued. o Combination inhalers are recommended to guarantee that the LABA is not taken without ICS, and to improve inhaler adherence. o In adults >18 years with a history of asthma attacks on medium dose ICS or ICS/LABA, a combined ICS/LABA inhaler can be considered for maintenance and reliever therapy. • Additional controller therapies: o If asthma control remains suboptimal after the addition of a LABA, then consider one of the following: ▪ Increase the dose of ICS from low dose to medium dose in adults or from very low dose to low dose in children (five to 12 years of age), if not already on these doses; or ▪ Consider adding a LTRA. • Specialist therapies: o All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care. o If control remains inadequate on medium dose ICS (adults) or low dose ICS (children) plus a LABA or a LTRA, the following interventions can be considered: ▪ Increasing the ICS to high dose (adults) or medium dose (children five to 12 years) ▪ Adding a LTRA (if not already trialed) ▪ Add tiotropium (adults) ▪ Add a theophylline. o If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose). o Continuous or frequent use of oral steroids: ▪ For patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control. ▪ Patients taking oral steroids long-term or frequently are at risk for developing systemic side effects and should be closely monitored.

Clinical Guidelines	Recommendations
	○ Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden. ○ Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden. ○ The use of immunotherapy is not recommended for the treatment of asthma in adults or children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the respiratory smooth muscle relaxants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Respiratory Smooth Muscle Relaxants[1-3]

Indication(s)	Aminophylline	Theophylline
Asthma		
Treatment of acute exacerbations of the symptoms and reversible airflow obstruction associated with asthma	✔ * (injection)	✔ * (injection)
Treatment of the symptoms and reversible airflow obstruction associated with asthma		✔
Chronic Bronchitis and Emphysema		
Treatment of acute exacerbations of the symptoms and reversible airflow obstruction associated with chronic bronchitis and emphysema	✔ * (injection)	✔ * (injection)
Treatment of the symptoms and reversible airflow obstruction associated with chronic bronchitis and emphysema		✔

*Indicated as an adjunct to inhaled beta-2 selective agonists and systemically administered corticosteroids.

IV. Pharmacokinetics

The pharmacokinetic parameters of the respiratory smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Respiratory Smooth Muscle Relaxants[2]

Generic Name(s)	Onset (hours)	Duration (hours)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-life (hours)
Aminophylline	IV: within minutes PO: 0.25 to 0.5	Variable	100	40	Liver (90)	Renal (10 to 13)	3.7 to 12.0*
Theophylline	ER: 8 IR: 0.25 to 0.5	Variable	Complete (% not reported)	40	Liver (90)	Renal (10)	3.7 to 12.0*

*Elimination half-life highly variable and dependent upon age, liver function, cardiac function, presence of lung disease, and smoking history.
ER=extended-release, IR=immediate-release, IV=intravenous, PO=oral

V. Drug Interactions

Major drug interactions with the respiratory smooth muscle relaxants are listed in Table 5.

Table 5. Major Drug Interactions with the Respiratory Smooth Muscle Relaxants[2]

Generic Name(s)	Interaction	Mechanism
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Halothane	Halothane may cause catecholamine-induced arrhythmias in a patient who has taken theophylline.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Quinolones	Inhibition of cytochrome P450 1A2 isoenzymes by quinolones may decrease the metabolic elimination of theophylline. Additional theophylline plasma concentration and clinical monitoring are indicated, as a dose reduction may be needed during concurrent therapy.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Adenosine	The pharmacologic effects of adenosine may be decreased by xanthines. Adenosine may lose its pharmacologic effect in patients treated with xanthines.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Barbiturates	Barbiturates may increase the metabolism and clearance of xanthines by inducing cytochrome P450 enzymes resulting in decreased asthma control.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	β-blockers (non-selective)	Non-selective β-blockers may decrease the elimination of xanthines by inhibiting the n-demethylation process resulting in increased pharmacologic and toxic effects of theophylline. However, the use of a non-selective β-blocker may also decrease the therapeutic effects of xanthine derivatives by pharmacologic antagonism resulting in increased airway resistance and poor asthma control.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Dipyridamole	Xanthines may attenuate the pharmacologic action of intravenous dipyridamole, leading to false negative dipyridamole-thallium-201 cardiac imaging studies.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Hydantoins	Pharmacologic effects of xanthines and hydantoins may be decreased since reduced plasma concentrations of xanthines and phenytoin may occur.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Lithium	The pharmacologic effects of lithium may be decreased by xanthines. The renal excretion of lithium may be increased by xanthines.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Mexiletine	Mexiletine may impair hepatic elimination and increase plasma concentrations of xanthines. Additive arrhythmogenic effects may also occur.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Nondepolarizing muscle relaxants	Xanthines may cause a dose-dependent reversal of neuromuscular blockade induced by a nondepolarizing relaxant.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Tacrine	Xanthines given concomitantly with tacrine increases the half-life of xanthines and plasma concentrations by approximately two-fold.
Respiratory smooth muscle relaxants (aminophylline, theophylline)	Zileuton	Zileuton increases serum levels of xanthines resulting in increased pharmacologic and toxic effects, possibly through the inhibition of theophylline metabolism.
Theophyllines (aminophylline, theophylline)	Cimetidine	The pharmacologic effects of xanthines may be increased by cimetidine. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability,

Generic Name(s)	Interaction	Mechanism
		and seizures may occur.
Theophyllines (aminophylline, theophylline)	Erythromycin	The pharmacologic effects of xanthines may be increased by erythromycin. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (aminophylline, theophylline)	Febuxostat	Plasma concentrations and pharmacologic effects of xanthines may be increased by febuxostat.
Theophyllines (aminophylline, theophylline)	Fluvoxamine	Fluvoxamine may increase the pharmacologic effects of xanthines. Elevated plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (aminophylline, theophylline)	Oral contraceptives	Pharmacologic effects of xanthines may be increased by oral contraceptives. Elevated theophylline plasma levels with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Theophyllines (aminophylline, theophylline)	Rifamycins	Rifamycins may increase xanthine metabolism and clearance by inducing cytochrome P450 resulting in decreased asthma control.
Theophyllines (aminophylline, theophylline)	Thiabendazole	Thiabendazole may increase serum levels of xanthines resulting in increased pharmacologic and toxic effects through an unknown mechanism.
Theophyllines (aminophylline, theophylline)	Ticlopidine	Ticlopidine may decrease the elimination of xanthines resulting in increased pharmacologic and toxic effects.
Theophyllines (aminophylline, theophylline)	Troleandomycin	Pharmacologic effects of xanthines may be increased. Elevated plasma levels with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.

VI. Adverse Drug Events

The most common adverse drug events reported with the respiratory smooth muscle relaxants are listed in Table 6. Due to the narrow therapeutic index of the xanthines, adverse events are dependent on the peak serum concentration. They are generally mild and transient with serum levels <20 µg/mL, whereas they are more common and severe when the serum concentration exceeds 20 µg/mL.[1,2]

Table 6. Adverse Drug Events (%) Reported with the Respiratory Smooth Muscle Relaxants[1-3]

Adverse Events	Aminophylline	Theophylline
Cardiovascular		
Arrhythmia	✔	✔
Bradycardia	✔	-
Cardiac arrest	✔	-
Circulatory failure	✔	✔
Extrasystoles	✔	✔
Hypotension	✔	✔
Palpitations	✔	✔
Premature ventricular contraction	✔	✔
Tachycardia	1 to 10	1 to 10
Central Nervous System		
Dizziness	✔	✔
Headache	✔	✔
Insomnia	<1	<1
Irritability	<1	<1
Nervousness	1 to 10	1 to 10

Adverse Events	Aminophylline	Theophylline
Reflex hyperexcitability	✔	✔
Restlessness	1 to 10	1 to 10
Seizure	<1	<1
Syncope	✔	-
Dermatological		
Allergic skin reactions	<1	-
Angioedema	✔	-
Flushing	✔	✔
Injection site pain	✔	-
Pruritus	✔	-
Rash	<1	-
Tissue sloughing	✔	-
Urticaria	✔	-
Endocrine and Metabolic		
Elevated serum glutamic oxaloacetic transaminase	✔	✔
Hyperglycemia	✔	✔
Syndrome of inappropriate antidiuretic hormone	✔	✔
Gastrointestinal		
Abdominal cramping	✔	✔
Anorexia	✔	✔
Diarrhea	✔	✔
Epigastric pain	✔	✔
Hematemesis	✔	✔
Nausea	1 to 10	1 to 10
Vomiting	1 to 10	1 to 10
Genitourinary		
Albuminuria	✔	✔
Diuretic effect	✔	✔
Excretion of renal tubular cells	✔	✔
Hematologic		
Bone marrow suppression	✔	✔
Hemorrhagic diathesis	✔	✔
Leukopenia	✔	✔
Thrombocytopenia	✔	✔
Laboratory Test Abnormalities		
Elevated plasma glucose	-	✔
Elevated uric acid	✔	✔
Elevated free fatty acid	-	✔
Elevated total cholesterol	-	✔
Elevated high density lipoprotein	-	✔
Elevated high density lipoprotein/low density lipoprotein ratio	-	✔
Elevated urinary free cortisol excretion	-	✔
Musculoskeletal		
Muscle cramps	-	✔
Respiratory		
Tachypnea	✔	✔
Other		
Dehydration	✔	✔
Tremor	<1	<1
Twitching of fingers/hands	✔	✔

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the respiratory smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Respiratory Smooth Muscle Relaxants[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aminophylline	Asthma, chronic bronchitis, and emphysema: Injection: initial, 6 mg/kg intravenous over 20 to 30 mins; maintenance, 0.5 mg/kg/hr continuous infusion ; maximum, 900 mg/day theophylline or 13 mg/kg/day theophylline, whichever is less	Asthma, chronic bronchitis, and emphysema: Injection: initial, 6 mg/kg IV over 20 to 30 mins; maintenance, 0.5 to 1 mg/kg/hr; maximum, 900 mg/day theophylline or 13 to 24 mg/kg/day theophylline, whichever is less	Injection: 250 mg/10 mL 500 mg/20 mL
Theophylline	Asthma, chronic bronchitis and emphysema: Elixir and solution: initial loading dose, 5 mg/kg; maintenance, 300 mg/day anhydrous theophylline in divided doses every 6 to 8 hours (may increase dose to 400 mg/day after 3 days, may increase dose to 600 mg/day after 3 more days); maximum, 900 mg/day, unless serum levels indicate need for larger doses Extended-release capsule: initial, 300 to 400 mg once daily; maintenance, may increase dose to 400 to 600 mg once daily after 3 days, if dose greater then 600mg/day, titrate according to blood levels Extended-release tablet: initial, 150 mg twice daily; maintenance, may increase dose to 200 mg twice daily after 3 days, may increase dose to 300 mg/day after 3 more days; maximum: 900 mg/day unless serum levels indicate need for larger doses Injection: initial, 4.6 mg/kg over 20 to 30 mins; maintenance, 0.3 to 0.4 mg/kg/hr continuous infusion; maximum, 900 mg/day unless serum levels indicate need for larger doses	Asthma, chronic bronchitis and emphysema: Elixir and solution: initial, 12 to 14 mg/kg/day in divided doses every 4 to 6 hours (maximum, 300 mg/day); after 3 days (if tolerated), increase to 16 mg/kg/day in divided doses every 4 to 6 hours, (maximum, 400 mg/day); after 3 more days (if tolerated and needed), increase to 20 mg/kg/day in divided doses every 4 to 6 hours; maximum, 600 mg/day Extended-release capsule: initial, 12 to 14 mg/kg/day; maintenance, may increase to 16 mg/kg once daily after 3 days, may increase to 20 mg/kg/day after 3 more days; if dose greater than 600 mg/day, titrate according to blood levels Extended-release tablet: initial, 12 to 14 mg/kg/day divided every 12 hours; maintenance, may increase to 16 mg/kg/day divided every 12 hours after 3 days, may increase to 20 mg/kg/day divided every 12 hours after 3 more days; maximum, 600 mg/day Injection: initial, 4.6 mg/kg	Elixir: 80 mg/15 mL Extended-release capsule: 100 mg 200 mg 300 mg 400 mg Extended-release tablet: 100 mg 200 mg 300 mg 400 mg 450 mg 600 mg Injection: 200 mg/50 mL 200 mg/100 mL 400 mg/250 mL 800 mg/250 mL Solution: 80 mg/15 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		over 20 to 30 mins; maintenance, 0.5 to 0.8 mg/kg/hr; maximum, 900 mg/day unless serum levels indicate need for larger doses	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the respiratory smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Respiratory Smooth Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asthma				
Yung et al.[9] (1998) Aminophylline IV 10 mg/kg loading dose, followed by continuous infusion of 1.1 mg/kg/hr (<10 years of age) or 0.7 mg/kg/hr (≥10 years of age) vs placebo	DB, PC, RCT Patients 1 and 19 years of age with severe acute asthma currently unresponsive to three 5 mg doses of nebulized albuterol and treated with large doses of inhaled albuterol (5 mg/dose in 4 mL at 8 to 10 L/min), inhaled ipratropium (250 µg every 4 to 6 hours), and IV steroids (1mg/kg every 6 hours, followed by oral prednisone 1 mg/kg BID during convalescence)	N=163 3 days	Primary: Length of hospital stay Secondary: Spirometry, FEV_1, FVC, maximum mid-expiratory flow, and PEFR, saturated oxygen, supplemental oxygen use, albuterol doses, intubation duration	Primary: The effects of aminophylline on the mean length of hospital stay was not statistically significant compared to placebo (2.69, 2.87, days, respectively; P=0.53). Secondary: Compared to placebo, there was a statistically significant difference in patients receiving aminophylline relative to improved FEV_1, maximum mid-expiratory flow, and PEFR at 6 hours, 12 to 18 hours, and 24 hours (except for maximum expiratory flow at 24 hours). P values ranged from 0.0016 to 0.043. Patients receiving aminophylline experienced a higher saturated oxygen level up to 30 hours compared to placebo. Exact P values not reported. Patients receiving placebo required a longer duration of supplemental oxygen compared to placebo (P=0.015), longer duration (P=0.045) and higher total dose (P=0.009) of IV albuterol. There was no statistical difference between the treatment groups in terms of number of doses of albuterol or reduction in intubation duration.
Vieira et al.[10] (1998) Aminophylline IV 6 mg/kg loading dose, followed by 1.2 mg/kg/hr	DB, PC, PRO, RCT Patients 1 to 7 years of age with moderate bronchoconstriction despite 3 sequential fenoterol*	N=43 12 to 14 hours	Primary: Wood-Downes clinical score Secondary: Protocol discharge, hospital admission rates	Primary: There is no significant difference between the aminophylline and placebo groups relative to hours needed to reach Wood-Downes score ≤2 in order to be discharged (12.5 and 14.6, respectively; P=0.13). Secondary: There is no significant difference between the treatment groups relative to protocol discharge (P=0.33) or hospital admission rates (P=0.59).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	nebulizations, history of 2 similar episodes, and Wood-Downes score between 3 and 6, persisting symptoms lasting ≥2 days			
Roberts et al.[11] (2003) Aminophylline infusion (5 mg/kg over 20 minutes), followed by 0.9 mg/kg/hr infusion vs albuterol IV bolus (15 µg/kg over 20 minutes), followed by saline infusion	DB, RCT Patients 1 to 16 years of age with acute severe asthma that is unresponsive to treatment with three nebulizers (combined albuterol [2.5 mg, 5 mg if ≥5 years] and ipratropium [125 µg, 250 µg if ≥5 years]) administered over 1 hour and systemic steroids	N=44 3 to 4 days	Primary: Asthma severity score, supplemental oxygen Secondary: Adverse effects	Primary: There was no significant difference in both treatment groups relative to asthma severity score at 2 hours (P=0.93) or change in this score from time 0 to 2 hours (P=0.85). Secondary: There was a significant difference in the albuterol group in terms of requiring a longer hospital stay (P=0.02). There was no significant difference in both treatment groups relative to adverse events (P=0.50) or longer duration of oxygen therapy (P=0.07).
Ream et al.[12] (2001) Aminophylline 7 mg/kg IV bolus, followed by theophylline infusion (to achieve serum levels between 12 to 17 µg/mL; age-related dosing protocol: 6 to 12 months 0.5	DB, PRO, RCT Patients between 13 months and 17 years with severe status asthmaticus admitted to the pediatric intensive care unit for ≤2 hours with intractable wheezing and a modified Wood-	N=47 29 to 189 days	Primary: Time to reach clinical asthma score ≤3 Secondary: Time required to meet predetermined criteria for discharge from pediatric intensive care unit, adverse	Primary: The patients receiving theophylline showed a statistically significant decrease in time to reach a clinical asthma score ≤3 (P<0.05), regardless of mechanical ventilation use. Secondary: There was a significant difference in time required to meet discharge criteria (P<0.05) and shortened length of intensive care unit stay observed in patients taking theophylline who were receiving mechanical ventilation relative (P<0.05). Theophylline was associated with more emesis (P<0.05) and the control regimen was associated with more tremor (P<0.05). Theophylline showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/hr, 1 to 9 years 0.8 mg/kg/hr, ≥10 years 0.65 mg/kg/hr) in addition to continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone vs continuous albuterol nebulization, intermittent, inhaled ipratropium, and IV methyl-prednisolone	Downes clinical asthma score of ≥5 and treated with an aggressive regimen consisting of continuous albuterol nebulization 0.3 mg/kg/hr at 7 to 8 L/min, intermittent inhaled ipratropium during first 48 hours of hospitalization at 250 to 500 µg every 6 hours, and IV methylprednisolone with bolus dose of 2 mg to 4 mg/kg, then 0.5 mg to 1.0 mg/kg/dose every 6 hours until discharge from intensive care unit		events	no statistically significant effect relative to the total incidence of side effects.
Yamauchi et al.[13] (2005) Theophylline 200 mg IV vs placebo	PG, RCT, SB Patients with mild acute exacerbation of bronchial asthma who were currently treated with oral SR theophylline and theophylline levels <13 µg/mL	N=22 2 hours	Primary: Spirometry and asthma symptoms (Borg Scale, wheezing index, coughing, and sputum production) Secondary: Not reported	Primary: There was a significant improvement in PEFR (from 313±82 to 356±111 L/min; P<0.005) and FEV_1 (from 1.66±0.48 L to 1.83±0.45 L; P<0.005) in patients receiving IV theophylline. There was a significant improvement in asthma symptoms, severity of asthma, Borg scale (P<0.05), wheezing index (P<0.05), coughing, and sputum production in patients receiving IV theophylline. Secondary: Not reported
Wheeler at al.[14] (2005) Theophylline IV	DB, PRO, RCT Patients between 3 and 15 years of age	N=40 4 to 5 days	Primary: Change in clinical asthma score over time	Primary: There was no clinically significant difference among the study groups in terms of improved change (P<0.05) in clinical asthma score over time.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bolus (6.4 mg/kg), followed by a continuous infusion and terbutaline IV bolus (20 µg/kg), followed by continuous infusion (0.4 µg/kg/hr) vs terbutaline IV bolus (20 µg/kg), followed by continuous infusion (0.4 µg/kg/hr) vs theophylline IV bolus (6.4 mg/kg), followed by a continuous infusion	who are critically ill with status asthmaticus and potential respiratory failure, admitted ≤2 hours; receiving continuous nebulized albuterol (10 mg/hr) and IV methylprednisolone (2 mg/kg every 6 hours for 24 hours followed by 1 mg/kg every 6 hours until discharge)		Secondary: Length of time to a clinical asthma score of ≤3, length of pediatric intensive care unit stay, progressive mechanical ventilation, incidence of adverse effects	Secondary: With the exception of more reported nausea in patients receiving both theophylline and terbutaline, there was no clinically significant difference among the study groups in terms of the incidence of adverse effects. There was also no significant difference in terms of the length of hospital stay. No patient required mechanical ventilation. When four patients were excluded from data analysis, a significant difference was seen in the shorter length of time to achieving ≤3 clinical asthma scores in patients receiving theophylline/placebo compared to terbutaline/placebo and theophylline/terbutaline (24.2±121 vs 51.6±33.3 vs 47.1±38.3 hours, respectively; P<0.05).
Helms et al.[15] (1983) Theophylline 10 mg/kg TID, followed by aminophylline SR 14 mg/kg BID vs aminophylline SR 14 mg/kg BID, followed by	DB, PG, XO Children between 7 and 13 years of age with chronic asthma and mean daily PEFR <75% of that predicted on stature over a 4 week assessment period	N=25 8 weeks	Primary: Pharmacokinetics and therapeutic effects (morning and evening PEFRs, weighted drug score, daily symptoms scores) Secondary: Not reported	Primary: There was no statistically significant difference in peak theophylline levels (P>0.05), morning and evening PEFRs (P>0.05), drug score (P>0.05), day wheeze (P>0.05), and cough (P>0.05) among treatment groups. There was a statistically significant difference in the increased daytime activity scores (P<0.05) and in the reduction of nighttime wheezing (P<0.05) in patients receiving the controlled release aminophylline compared to the standard oral theophylline. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
theophylline 10 mg/kg TID vs theophylline 10 mg/kg TID vs aminophylline CR 14 mg/kg BID				
Dombrowski et al.[16] (2004) Theophylline 400 to 800 mg/day (to achieve serum level between 8 to 12 µg/mL) vs beclomethasone inhaler 4 puffs TID	DB, PC, PRO, RCT Pregnant women <26 weeks' gestation with mild or moderate asthma	N=385 Less than 26 weeks' gestation until delivery	Primary: Proportion of patients with at least one asthma exacerbation required medical intervention, oral corticosteroids, or hospitalization Secondary: Treatment failures, participant withdrawal, delivery and perinatal outcomes	Primary: There was no significant difference in the proportion of women receiving either theophylline tablets or inhaled beclomethasone (20.4 and 18.0%, respectively; P=0.554) relative to experiencing at least 1 validated asthma exacerbation during the study. Secondary: There was no significant difference in the proportion of women receiving either theophylline tablets or inhaled beclomethasone relative to treatment failure (3.7 and 2.1%, respectively; P=0.896) and all obstetric outcomes (P values ranged from 0.160 to 0.962). Women receiving theophylline tablets were more likely to discontinue their medications due to side effects compared to those women receiving inhaled beclomethasone (RR, 0.3; 95% CI, 0.1 to 0.9; P=0.016).
Reed et al.[17] (1998) Theophylline SR 100 to 300 mg (to achieve a serum level between 8 to	DB, DD, MC, RCT Patients between 6 and 65 years of age with asthma associated with symptoms of	N=747 12 months	Primary: Daily diary symptoms; PEFR; supplemental bronchodilator use; doctor's office or hospital	Primary: Compared to theophylline, treatment with beclomethasone resulted in a greater reduction in symptom scores (P=0.002 at six months), symptoms days (P=0.002 at six months), supplemental bronchodilator use (P=0.038 at six months), systemic glucocorticoid doses (P=0.009 at six months), bronchial hyperresponsiveness (P<0.05 at six months; P<0.001 at one year), and eosinophilia (P=0.001 at one year).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
15 µg/mL) vs beclomethasone inhaler 2 inhalations (42 mg/inhalation) QID	dyspnea, cough, and wheezing, and the need for a bronchodilator despite allergen avoidance; FEV_1 greater than 50% of predicted value before bronchodilator use and FEV_1 increased by 15% after bronchodilator use		visits and absence from work or school; spirometry; methacholine testing; adverse experiences; cortical blood measurements Secondary: Not reported	There was no overall statistical difference between theophylline and beclomethasone in all other primary study parameters. Compared to beclomethasone, theophylline use was associated with a greater discontinuation of therapy (3 and 6%, respectively) due to side effects, including headache, nervousness, insomnia, and gastrointestinal problems. Compared to theophylline, beclomethasone use was associated with more oropharyngeal candidiases, hoarseness, and reduced morning plasma cortisol levels before and after cosyntropin. Secondary: Not reported
Tinkleman et al.[18] (1994) Theophylline SR administered BID (to achieve serum levels between 8 to 15 µg/mL) vs beclomethasone inhaler 2 inhalations (42 µg/inhalation) QID	DB, DD, MC, RCT Children between 6 and 16 years of age with mild to moderate chronic asthma, FEV_1 greater than 50% of predicted and increased FEV_1 by 15% after bronchodilator use	N=195 12 months	Primary: Daily diary symptom record, PEFR, supplemental bronchodilator and glucocorticoid use, doctor/hospital visits, school/work absence, physician's global evaluation, side effects Secondary: Not reported	Primary: Theophylline and beclomethasone led to improvements in overall asthma control (symptom diaries, PEFR, methacholine response, pre-/post-bronchodilator FEV_1, doctor/hospital visits, school/work absences, and physician's global evaluation). Compared to theophylline, beclomethasone use was associated with less bronchodilator use (P=0.004 at month five, P=0.025 at month six, P=0.003 at month 10) and fewer milligrams of systemic corticosteroid use (123.9 mg, 58.4 mg, respectively; P=0.002). Compared to beclomethasone, theophylline use was associated with more adverse events: headache (P=0.001), central nervous system changes (P=0.008), tremor (P=0.003), gastric irritation (P=0.013), and nausea/vomiting (P=0.016). Beclomethasone was associated with a slower of growth velocity compared to theophylline in all children (4.2 and 5.5 cm/yr, respectively; P=0.005) and in prepubescent males only (4.3 and 6.2 cm/yr, respectively; P=0.005). Secondary: Not reported
Ukena et al.[19]	DB, PG, RCT	N=133	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1997) Theophylline 250 to 375 mg BID and beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 400 µg BID	Patients with mild to moderate asthma with FEV_1 of 50 to 85% predicted normal and FEV_1 increase of 15% after bronchodilator who remained symptomatic on beclomethasone 400 µg/day or equivalent ICS dose	6 weeks	Improvement of PEFR at six weeks over baseline Secondary: Asthma symptoms, albuterol use	Both theophylline/beclomethasone and beclomethasone regimens demonstrated equal efficacy in increasing FEV_1 and PEFR at week six ($P<0.01$). There was no significant difference between the treatment groups ($P=0.960$). Secondary: There was no significant difference in daytime ($P=0.575$) or nighttime ($P=0.196$) asthma symptoms between theophylline and beclomethasone and beclomethasone regimens. There was no significant difference in the reduction of albuterol use during the daytime ($P=0.392$) or nighttime ($P=0.814$) between theophylline and beclomethasone and beclomethasone regimens.
Lim et al.[20] (2000) Theophylline SR 200 mg BID and beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 200 µg BID vs beclomethasone inhaler 500 µg BID	DB, PG, RCT Patients between 18 and 65 years old with asthma, with PEFR greater than 50% of predicted normal and PEFR increase of 15% after bronchodilator use and who remained symptomatic despite use of low-dose ICS and as needed albuterol	N=155 6 months	Primary: Mean morning and evening PEFR Secondary: Diurnal variation of PEFR, use of short-acting β_2-agonist, symptom scores, asthma exacerbations, quality of life	Primary: Significant improvement was observed in mean morning PEFR in patients receiving high-dose beclomethasone ($P=0.007$) and low-dose beclomethasone and theophylline ($P=0.006$). Significant improvement was observed in mean evening PEF in patients receiving low-dose beclomethasone and theophylline ($P=0.002$). There was no significant difference among the three study groups relative to change in morning and evening PEFR. Secondary: There was no significant difference among the three study groups relative to diurnal variation of PEFR, symptom scores, or short-acting β_2-agonist usage, asthma exacerbations, quality of life, or side effects.
Wang et al.[21] (2005) Theophylline SR 200 µg BID and beclomethasone inhaler	OL, PG, RCT Patients between 18 and 70 years old with asthma showing FEV_1 increase of greater	N=41 6 weeks	Primary: Lung function testing, sputum induction (cell differential counts and interleukin-5), PEFR, symptom	Primary: Both the beclomethasone and beclomethasone and theophylline groups experienced improved mean morning and evening PEFR ($P<0.001$, $P<0.05$, respectively) and FEV_1 ($P<0.05$), as well as a reduction in symptom score ($P<0.001$), β_2-agonist usage ($P<0.01$), percentage eosinophils ($P<0.001$), and interleukin-5 levels ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
250 µg BID vs beclomethasone inhaler 500 µg BID	than 15% and 20 mL over baseline after bronchodilator use and use of an ICS with a dose ≤1,000 µg		score, β_2-agonist use Secondary: Not reported	There was no significant difference in all primary study parameters between the two treatment groups. Both treatment regimens were well tolerated. Secondary: Not reported
Spears et al.[22] (2009) Theophylline 400 mg QD and beclomethasone inhaler 200 µg QD vs theophylline 400 mg QD vs beclomethasone inhaler 200 µg QD	DB, DD, PG, RCT Patients 18 to 60 years of age with mild to moderate asthma who were current smokers and who were receiving ≤1,000 µg/day of beclomethasone (or equivalent)	N=68 4 weeks	Primary: Change in lung function and ACQ scores Secondary: Inflammatory biomarkers in sputum	Primary: The addition of theophylline to inhaled beclomethasone resulted in statistically significant improvements in morning PEF (P=0.008) and ACQ scores (-0.47; 95% CI, -0.91 to -0.04). Theophylline monotherapy did not improve lung function, except for post-bronchodilator FVC (304 mL; P=0.046). However, it did improve the ACQ scores after four weeks (-0.55; 95% CI, -0.99 to -0.11). Secondary: Treatment with the combination of theophylline and inhaled beclomethasone was associated with a reduction in the mean absolute (-10.99; P=0.018) and percentage sputum lymphocyte count. Theophylline alone was associated with reductions in sputum supernatant interleukin-8 (P=0.009) and myeloperoxidase (P=0.026).
Morali et al.[23] (2001) Theophylline 200 mg BID vs budesonide inhaler 2 inhalations (800 µg) BID	DB, PG, RCT Patient between 18 and 45 years old with mild to moderate asthma with baseline FEV_1 greater than 60% of predicted value and FEV_1 increased by 20% after bronchodilator use	N=38 4 weeks	Primary: Clinical, functional, anti-inflammatory effects Secondary: Not reported	Primary: Budesonide use was associated with a significant reduction in serum interleukin levels (P<0.0005), eosinophil counts (P<0.005), daytime (P<0.01) and nighttime (P<0.005) symptom scores; increase in morning (P<0.005) and evening PEFR (P<0.05 and FEV_1 (P<0.01). Theophylline use was associated with a statistically significant reduction in serum interleukin levels (P<0.05), nasal eosinophil counts (P<0.01) blood eosinophil counts (P<0.02), and daytime/nighttime symptom scores (P<0.05). There were no significant differences between theophylline and budesonide.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Evans et al.[24] (1997) Theophylline 250 to 375 mg BID and budesonide inhaler 400 µg BID vs budesonide inhaler 800 µg BID	DB, PC, RCT Patients 18 to 67 years of age with asthma, FEV_1 of 50% predicted and FEV_1 increase of 15% after bronchodilator, who were uncontrolled despite 800 to 1000 µg budesonide or equivalent ICS dose	N=62 3 months	Primary: PEFR, albuterol usage, 4-point scale for symptom severity Secondary: Not reported	Primary: Compared to budesonide, the budesonide/theophylline group demonstrated greater improvements in FEV_1 (P=0.03) and FVC (P=0.03). There was no significant difference in PEFR (P=0.16), daytime (P=0.57) and nighttime (P=0.97) bronchodilator use, daytime (P=0.26) and nighttime (P=0.59) symptoms. Budesonide reduced serum cortisol concentrations; however, this was no significantly different than budesonide/theophylline therapy (P=0.09). Both treatment groups were well tolerated. Secondary: Not reported
Yurdakul et al.[25] (2003) Theophylline SR 400 mg QD vs budesonide inhaler 400 µg QD vs montelukast tablet 10 mg QD	PG, RCT Patients aged 23 and 45 years old with mild persistent asthma, FEV_1 at least 80% of the predicted normal value and FEV_1 increase of 15% after 400 µg of albuterol	N=74 3 months	Primary: Lung function (PEFR, FEV_1), asthma symptom scores, supplemental β_2-agonist use, adverse events, asthma exacerbations Secondary: Not reported	Primary: FEV_1 and PEFR values were not significantly different among treatment groups at the end of the study (P >0.05 and P >0.05, respectively). Asthma symptom scores and supplemental β_2-agonist use were not significantly different (P >0.05) among treatment groups. The adverse events for montelukast, theophylline, and budesonide were 12.0, 16.0, and 16.7%, respectively. Asthma exacerbation percentage for montelukast, theophylline, and budesonide were 16.0, 12.5, and 0%. Secondary: Not reported
Furukawa et al.[26] (1984) Theophylline SR	DB, PC, RCT Patients between 5 and 15 years old	N=46 3 months	Primary: Home assessment (symptom, PEFR), office	Primary: Both theophylline and cromolyn demonstrated similar effects relative to symptom scores, increased pulmonary function, and decreased use of the bronchodilator.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 to 300 mg BID (to achieve serum levels between 10 to 15 µg/mL) vs cromolyn sodium inhaler QID	with daily asthma symptoms of coughing, chest congestion, or wheezing and FEV_1 greater than 20% at methacholine challenge and naïve to regular asthma medication		assessment (FVC, FEV_1, PEFR, and forced mid-expiratory flow rate, asthma score) Secondary: Not reported	Compared to cromolyn, theophylline use was associated with more side effects (nausea, nervousness; P<0.02) and doctor visits (P<0.01). Secondary: Not reported
Hendeles et al.[27] (1995) Theophylline SR every morning (to achieve serum levels between 10 to 20 µg/mL) vs cromolyn inhaler 2 inhalations QID vs placebo	DB, DD, RCT, XO Patients between 18 and 35 years old with intermittent to mild chronic asthma with an allergic component, FEV_1 greater than 65% of predicted, 20% decrease in FEV_1 after 8 mg/mL inhaled histamine, and a dual response to inhaled allergen and histamine	N=16 7 days	Primary: FEV_1, airway responsiveness to histamine Secondary: Not reported	Primary: During the late phase, decrease in mean FEV_1 for placebo, theophylline, and cromolyn were 30, 16, and 13%, respectively. There was a significant difference in the mean FEV_1 for theophylline and cromolyn compared to placebo (P=0.0001), but no significant difference for theophylline vs cromolyn (P=0.1). Geometric mean fold rise in airway responsiveness for placebo, theophylline and cromolyn were 3.0, 1.7, and 1.5, respectively. There was a significant difference in the mean airway responsiveness with theophylline and cromolyn compared to placebo (P=0.0001), but no significant difference for theophylline vs cromolyn (P=0.1). Secondary: Not reported
Burki et al.[28] (1997) Theophylline 300 to 700 mg (to achieve serum levels between 10 to 20 µg/mL) and ipratropium inhaler (40 µg)	DB, PC, RCT, XO Patients with mild to moderate stable asthma with FEV_1 of 70% of the predicted normal and a FEV_1 increase of 15% within 30 minutes of 2	N=19 7 days	Primary: Efficacy Secondary: Not reported	Primary: Both theophylline and ipratropium were effective in management of asthma control by increasing FVC (P<0.05) and FEV_1 (P<0.05). After three hours, treatment with theophylline/ipratropium led to a significantly greater increase in FEV_1 than theophylline or ipratropium monotherapy (3.00, 2.48, 2.61 L, respectively; P<0.05). There were no significant differences in side effects when comparing all study regimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs theophylline 300 to 700 mg (to achieve serum levels between 12 to 18 µg/mL) vs ipratropium inhaler (40 µg) vs placebo	inhalations of isoproterenol			Secondary: Not reported
Yurdakul et al.[29] (2002) Theophylline SR 400 mg QD and budesonide inhaler 400 µg BID vs formoterol inhaler 9 µg BID and budesonide inhaler 400 µg BID vs zafirlukast 20 mg BID and budesonide inhaler 400 µg BID	OL, PG, RCT Patients with moderate persistent asthma with symptoms despite treatment with moderate to high doses of ICS, who demonstrated FEV_1 increase of 15% after bronchodilator use	N=64 3 months	Primary: PEFR variability, FEV_1, daytime and nighttime asthma symptom scores, supplemental terbutaline use, asthma exacerbations, adverse effects Secondary: Not reported	Primary: Overall, there was no statistical difference between the treatment groups in terms of study outcome parameters (P>0.05). A greater percentage of patients receiving zafirlukast experienced medication-related side effects compared to formoterol and theophylline (31.6, 20.0, and 20.0%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vatrella et al.[30] (2005) Theophylline SR 600 mg x 1 dose vs salmeterol 50 µg x 1 dose vs theophylline SR 600 mg and salmeterol 50 µg x 1 dose vs placebo	PC, RCT, SB, XO Patients with moderate to severe asthma	N=10 4 days	Primary: Changes in FEV_1 Secondary: Not reported	Primary: Patients receiving salmeterol had a better clinical response compared to theophylline (based on earlier onset, greater magnitude, and longer duration). There were no P values reported comparing active treatments to each other for the mentioned parameters. Theophylline offered a synergistic improvement in FEV_1 values when taken concurrently with salmeterol in the 4^{th}, 6^{th}, and 8^{th} hours of the study, at which therapeutic plasma concentrations of theophylline were reached (P=0.05, P=0.03, P=0.05, respectively). Secondary: Not reported
Nutini et al.[31] (1998) Theophylline SR 150 mg BID (to achieve plasma levels between 10 to 20 µg/mL) vs salmeterol 50 µg BID	MC, OL, PG, RCT Patients ≥18 years of age with asthma, FEV_1 between 50 to 80% predicted value, FEV_1 increase of 15% after 200 µg of albuterol, and total symptom score ≥2	N=112 12 months	Primary: PEFR, symptom score, and additional albuterol use Secondary: The effects on quality of life of salmeterol and theophylline were evaluated by examining a synthetic score ranging from a minimum of 0 to	Primary: There was no significant difference in morning and evening PEFRs among the treatment groups. Salmeterol demonstrated greater efficacy compared to theophylline in controlling both daytime and nighttime asthma symptoms (P<0.001) and in reducing additional albuterol requirement (P<0.001). Secondary: The effects of salmeterol and theophylline in increasing quality of life showed no significant difference; both agents improved quality of life.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			maximum of 20	
Dawson et al.[32] (1986) Theophylline SR 10 mg/kg BID vs theophylline syrup 5 mg/kg QID	OL, PRO Children with chronic asthma requiring continuous bronchodilator therapy	N=61 3 months	Primary: Symptoms (night wheeze and cough, exercise-induced symptoms, daytime cough and wheeze), compliance, side effects, β_2-agonist usage Secondary: Not reported	Primary: There was no statistical difference in compliance or symptom control among treatment groups. There was a significant difference in greater side effects ($P<0.015$) and increased need for nebulizations with a β_2-agonist ($P<0.05$) in patients receiving theophylline microspheres compared to theophylline syrup. Secondary: Not reported
Schwartz et al.[33] (1998) Theophylline SR 200 to 400 mg BID (to achieve serum levels of 8 to 15 µg/mL) vs zileuton 400 mg QID	AC, DB, MC, PG, RCT Patients 18 and 60 years old with moderate asthma, FEV_1 40 to 80% of the predicted normal value and FEV_1 increase of 15% after β_2- agonist	N=377 13 weeks	Primary: Mean percentage change in FEV_1 from baseline to maximum improvement on days 36 and 92 of study Secondary: morning/evening PEFR, β_2-agonist use, asthma symptom scores, quality of life indexes (activity, symptoms, emotional changes, allergen exposure), drug tolerability	Primary: Mean percentage change in FEV_1 from baseline values to any postdose time-point was not significantly different among the treatment groups. Secondary: Morning and evening PEFR were not significantly different among treatment groups, although the mean evening change in PEFR for theophylline was greater than for zileuton 600 mg in the first two week comparison (95% CI, -33.5 to 4.9). On day 64 of the study, the difference in FEV_1 percentage change after β_2-agonist use was clinically significant for the theophylline and zileuton 400 mg groups (23 and 30%, respectively; $P=0.01$) The use of a β_2-agonist was significantly less in the theophylline group compared to the zileuton group within the first 10 weeks of the study only. Asthma symptom scores and quality-of-life indexes were not significantly different among the treatment groups. One or more adverse events associated with treatment were reported in zileuton 400 mg, zileuton 600 mg, and theophylline groups (121, 117, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				110, respectively). The clinical significance is unknown.
Faillers et al.[34] (1978) Theophylline elixir (150 mg) 5.5 mg/kg, ephedrine hydrochloride (25 mg) 0.93 mg/kg, guaifenesin 100 mg, and butabarbital 20 mg/15 mL; complete dosing regimen not specified vs theophylline elixir (150 mg) 5.5 mg/kg and guaifenesin 90 mg/ 15 mL; complete dosing regimen not specified vs elixir with ephedrine hydrochloride (25 mg) 0.93 mg/kg and butabarbital 20 mg/15 mL; complete dosing regimen not specified	DB, XO Children between 6 to 15 years old diagnosed with uncomplicated bronchial asthma with a FEV_1 between 30 to 75% and improved FEV_1 by ≥20% after inhaled isoproterenol	N=20 18 days	Primary: Pulmonary function tests (FEV_1, FVC, $FEV_{25\text{ to }75\%}$, FEF_{max}, FRC, Raw, TGV, Gaw/V_L) Secondary: Not reported	Primary: There was no statistical difference in all pulmonary function test parameters (FEV_1, FVC, $FEV_{25\%-75\%}$, FEF_{max}, FRC, Raw, TGV, Gaw/V_L) in patients receiving guaifenesin compared to placebo. Compared to placebo, patients receiving the theophylline, ephedrine, guaifenesin, and butabarbital combination product experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), $FEV_{25\%-75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), FRC ($P<0.05$), Raw ($P<0.05$), TGV($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to placebo, patients receiving the theophylline and guaifenesin combination product only experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), $FEV_{25\%-75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), FRC ($P<0.05$), Raw ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to placebo, patients receiving ephedrine and butabarbital experienced statistically significant improvements in FEV_1 ($P<0.05$), $FEV_{25\%-75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), FRC ($P<0.05$), Raw ($P<0.05$), TGV ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to placebo, patients receiving ephedrine experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), and $FEV_{25\text{ to }75\%}$ ($P<0.05$). Compared to patients receiving ephedrine-butabarbital, patients receiving theophylline, ephedrine, guaifenesin and butabarbital experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), $FEV_{25\text{ to }75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), FRC ($P<0.05$), Raw ($P<0.05$), TGV($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to patients receiving ephedrine and butabarbital, patients receiving ephedrine experienced statistically significant improvements in only FEV_1 ($P<0.05$). Compared to patients receiving ephedrine, patients receiving theophylline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs elixir with guaifenesin 100 mg/15 mL; complete dosing regimen not specified vs elixir with ephedrine hydrochloride (25 mg/15 mL) 0.93 mg/kg; complete dosing regimen not specified vs placebo elixir				and guaifenesin experienced statistically significant improvements in FEV_1 ($P<0.05$), FEF_{max} ($P<0.05$), Raw ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to patients receiving guaifenesin, patients receiving theophylline-guaifenesin experienced statistically significant improvements in FEV_1 ($P<0.05$), FVC ($P<0.05$), $FEV_{25\%-75\%}$ ($P<0.05$), FEF_{max} ($P<0.05$), Raw ($P<0.05$), and Gaw/V_L ($P<0.05$). Compared to patients receiving theophylline-guaifenesin, patients receiving theophylline-ephedrine-guaifenesin-butabarbital experienced statistically significant improvements in FRC ($P<0.05$) only. Secondary: Not reported
Chronic Obstructive Pulmonary Disorder				
Duffy et al.[35] (2005) Aminophylline IV 5 mg/kg loading dose, followed by 0.5 mg/kg/hr infusion (to achieve goal theophylline serum levels) vs	DB, PC, RCT Patients between 40 and 80 years old admitted due to a non-acidotic exacerbations of COPD with $FEV_1<70\%$ predicted, $FEV_1/FVC<7\%$ predicted, 20 pack-years smoking	N=132 5 days	Primary: Change in post-bronchodilator FEV_1 Secondary: Self-reported breathlessness, arterial blood gas tensions, FVC, length of hospital stay	Primary: There was no significant difference between the treatment groups relative to FEV_1 ($P=0.49$). Secondary: Compared to placebo, aminophylline demonstrated a significant difference in its effects relative to increased arterial pH ($P=0.001$) and reduction on arterial carbon dioxide tension ($P=0.01$). There was no significant difference between the treatment groups relative to self-reported breathlessness ($P=0.56$), FVC ($P=0.49$), or length of hospital stay ($P=0.19$).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	history, COPD symptoms for the last 24 hours			Aminophylline was associated with more nausea compared to placebo (44 vs 22%, respectively; P<0.05).
Rice et al.[36] (1987) Aminophylline IV 0 mg/kg (if last theophylline dose <6 hours ago) or 3 mg/kg (if last theophylline dose ≥6 hours ago) or 6 mg/kg (theophylline-naïve or if last theophylline dose >12 hours ago) as a loading dose, followed by a 0.5 mg/kg/hr infusion (to achieve adequate theophylline serum levels) vs placebo Patients were also treated with metaproterenol, methyl-prednisolone, ampicillin, and supplemental oxygen (as needed).	DB, PC, RCT Patients admitted due to an exacerbation of COPD with FEV_1 greater than 2 standard deviations below the predicted and FEV_1/FVC <60%	N=30 2 hours	Primary: FEV_1, FVC, dyspnea index, adverse events Secondary: Not reported	Primary: Both treatment groups demonstrated statistically significant improvements in FEV_1, FVC, and dyspnea (P<0.05). However, there was no significant difference between the treatment groups relative to these improvements (P>0.5). Aminophylline was associated with more gastrointestinal side effects compared to placebo (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jenkins et al.[37] (1982) Aminophylline SR 325 mg BID vs theophylline SR 250 mg BID vs placebo	SB, XO Male patients between 51 to 73 years old with chronic bronchitis and 5 to 15% reversibility of airway obstruction after 200 µg of inhaled albuterol	N=20 6 weeks	Primary: PEFR, daily symptom score (cough, wheeze, chest tightness), β-agonist inhaler usage Secondary: Not reported	Primary: There was no significant difference in morning or evening PEFRs (P value range of 0.58 to 0.95), β_2-agonist inhaler usage, and symptoms scores among treatment groups. Secondary: Not reported
Rossi et al.[38] (2002) Theophylline SR 200 to 300 mg BID (to achieve serum levels between 8 to 20 µg/mL) vs formoterol inhaler 12 µg BID vs formoterol inhaler 24 µg BID vs placebo	MC, PC, PG, RCT Patients >40 years of age with symptomatic COPD (FEV_1 <70% of predicted value and ≥0.75L, FEV_1/FVC <88% predicted [men] or <89% predicted [women])	N=854 12 months	Primary: AUC for FEV_1 Secondary: Standardized AUC for FVC, FEV_1, PEFR, symptom score, daily puffs of rescue inhaler, frequency of exacerbations, quality of life	Primary: Compared to placebo, there was a significant improvement in the AUC for FEV_1 over 12 hours for both doses of formoterol and theophylline treatment groups after three to 12 months of treatment (P<0.001). Secondary: Compared to placebo, there was a significant improvement for both formoterol and/or theophylline treatment groups in terms of quality of life symptom sub-scores (P=0.009 for 12 µg, P=0.016 for 24 µg, P=0.003 for theophylline), AUC for FVC (P<0.001, P≤0.007, respectively), 12-month PEF values (P<0.001, P<0.007, respectively), reduction in bronchodilator use (P≤0.003 for formoterol), frequency of exacerbations (P<0.008, no P value, respectively), need for additional COPD therapy (P=0.043 for 24 µg dose, P=0.019, respectively). Compared to theophylline, formoterol use was associated with a significantly greater reduction in AUC for FVC at three months (P≤0.016) and 12-month PEF values (P≤0.020). There was no significant difference between the treatment groups relative to average symptoms score. Patients receiving theophylline experienced a significant increased risk for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				discontinuing treatment compared to placebo (P=0.002), formoterol 12 µg (P=0.001), and formoterol 24 µg (P=0.001). Compared to theophylline, both doses of formoterol was overall more effective (P≤0.026).
Crimi et al.[39] (1995) Theophylline SR 250 mg BID for 4 days, then 350 mg BID thereafter (to achieve serum levels of 10 to 20 µg/mL) vs nedocromil sodium 2 inhalations QID	DB, DD, PG, RCT Patients between 18 and 76 years old with chronic reversible obstructive airway disease	N=105 6 weeks	Primary: Daytime and nighttime symptoms, inhaled bronchodilator use, morning tightness, cough, PEFR Secondary: Not reported	Primary: There was no overall significant difference in improvements in patients receiving either theophylline or nedocromil relative to mean pulmonary function measurements, inhaled bronchodilator use, symptom severity, or clinician's assessment of disease severity. Theophylline demonstrated a greater reduction in morning tightness and nighttime inhaled bronchodilator use at weeks 1 and 2 when compared to nedocromil. There was a greater number of gastrointestinal side effects (P<0.05) and central nervous system related events (P<0.01) in patients receiving theophylline compared to nedocromil. Secondary: Not reported
Broseghini et al.[40] (2005) Theophylline SR (to achieve serum levels between 10 to 20 µg/mL) vs salmeterol 50 µg BID vs salmeterol 100 µg	DB, DD, RCT, XO Patients with stable moderate to severe COPD with cough and sputum history, FEV_1 between 30% and 70% of predicted normal, and poor reversibility (FEV_1 increase <12% and <200 mL from baseline after bronchodilator use)	N=13 22 weeks	Primary: Pulmonary function tests, PEFR, adverse effects Secondary: Not reported	Primary: Compared to placebo, there was a greater increase in FEV_1 (P<0.01), FVC (P<0.05), and morning PEFR (P<0.01 for salmeterol 100 µg) in patients receiving salmeterol. Compared to placebo, there was a significant improvement in FEV_1 in patients receiving salmeterol (P<0.01) and theophylline (P<0.05). There was no significant difference between salmeterol and theophylline relative to FEV_1. There was no statistical difference in primary study endpoints between the two inhaled salmeterol doses (P=0.867). Overall, both treatment regimens were well tolerated with no significant difference.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs placebo				Secondary: Not reported
ZuWallack et al.[41] (2001) Theophylline SR 100 mg BID (to achieve serum levels between 10 to 20 µg/mL) and salmeterol 42 µg BID vs theophylline SR 100 mg BID (to achieve serum levels between 10 to 20 µg/mL) vs salmeterol 42 µg BID	DB, DD, PG, RCT Patients >45 years of age with COPD, FEV_1 ≥0.7 L, FEV_1 ≤65% of predicted, and FEV_1/FVC ratio ≤70%	N=943 12 weeks	Primary: Change from baseline in AUC for FEV_1, predose FEV_1 and FVC Secondary: PEFR, symptoms scores, albuterol use, COPD exacerbations, quality of life	Primary: There was a significant improvement observed with salmeterol and theophylline, salmeterol monotherapy, and theophylline monotherapy treatment groups in terms of mean pre-dose FEV_1 and FVC (P<0.001, P<0.001, P≤0.021 except for FVC at week 12, respectively). Treatment with salmeterol and theophylline was associated with greater improvement in FEV_1 and FVC (P<0.020) compared to salmeterol monotherapy and theophylline monotherapy. Secondary: Treatment with salmeterol/theophylline was associated with a greater improvement in dyspnea symptom reduction (P≤0.048), albuterol use reduction (P≤0.048), COPD exacerbations (P=0.023 vs placebo), more symptom-free days (P=0.023 vs theophylline), and mean overall change from baseline in quality of life (P≤0.019) compared to salmeterol only and theophylline only treatment groups. There was a significant association with fewer side effects in patients receiving salmeterol compared to either treatment containing theophylline (P≤0.028).
Cazzola et al.[42] (2004) Theophylline SR BID (to achieve serum levels between 10 to 20 µg/mL) and fluticasone 500 µg	OL, RCT Patients >50 years of age with at least a 20-year smoking history, FEV_1<70% of predicted but more than 0.5 L and FEV_1/FVC ratio	N=66 4 months	Primary: Pulmonary function, dyspnea, supplemental albuterol use Secondary: Not reported	Primary: Both treatment groups demonstrated improvements in FEV_1 (P<0.05); there was no difference between the groups relative to pulmonary function tests (P>0.05). The salmeterol-fluticasone group experienced statistically significant greater reduction in dyspnea episodes and supplemental albuterol use compared to the theophylline and fluticasone group (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs salmeterol-fluticasone 50-500 µg BID (fixed-dose combination product)	<70% after albuterol 400 µg			Secondary: Not reported
Cazzola et al.[43] (2000) Theophylline BID (to achieve goal serum levels) and salmeterol 50 µg BID vs salmeterol 50 µg BID vs salmeterol 50 µg and fluticasone 250 µg BID vs salmeterol 50 µg and fluticasone 500 µg BID	OL, RCT Patients ≥50 years of age with at least a 20-year smoking history and well-controlled COPD that was previously treated with slow-release theophylline; change in FEV_1 ≤12% of predicted normal after albuterol 400 µg, FEV_1 post-bronchodilator <85%, and good metered-dose inhaler technique	N=80 3 months	Primary: FEV_1, FVC Secondary: Not reported	Primary: All treatment groups demonstrated statistically significant gradual improvements in FEV_1 ($P<0.05$). Salmeterol 50 µg/fluticasone 500 µg group demonstrated a statistically significant difference in its greater effect on FEV_1 compared to salmeterol and theophylline and salmeterol only treatment groups ($P<0.05$). Secondary: Not reported
Devereux et al.[44]	DB, PC, RCT	N=1,567	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2018) Theophylline (200 mg once or twice per day) to provide plasma concentrations of 1 to 5 mg/L vs placebo Treatment in addition to current therapy that included ICS	Patients ≥40 years of age with COPD, at least two exacerbations in the previous year, FEV_1/FVC of <0.7, smoking history of more than 10 pack-years, and current use of ICS	1 year	Number of COPD exacerbations requiring antibiotics, oral corticosteroids, or both (as reported by the patient) Secondary: Hospital admissions, spirometry, safety	There were 1727 exacerbations in the theophylline group (mean, 2.24; 95% CI, 2.10 to 2.38 exacerbations per year) vs 1703 in the placebo group (mean, 2.23; 95% CI, 2.09 to 2.37 exacerbations per year); unadjusted mean difference, 0.01 (95% CI, -0.19 to 0.21) and adjusted incidence rate ratio, 0.99 (95% CI, 0.91 to 1.08). Secondary: There were 0.17 mean COPD hospital admissions per participant in the theophylline group and 0.24 in the placebo group (mean difference, −0.07; 95% CI, −0.13 to −0.01). At week 52, the mean Fev_1 % predicted was 51.5 in the theophylline group and 52.1 in the placebo group (marginal mean difference, −0.57; 95% CI, −2.51 to 1.36). Serious adverse events in the theophylline and placebo groups included cardiac, 2.4% vs 3.4%; gastrointestinal, 2.7% vs 1.3%; and adverse reactions such as nausea (10.9% vs 7.9%) and headaches (9.0% vs 7.9%).
Jenkins et al.[45] (2021) TASCS Theophylline 100 mg twice daily plus prednisone 5 mg once daily vs theophylline 100 mg twice daily vs placebo	DB, PC, MC, RCT Patients 40 to 80 years of age with a diagnosis of stable moderate to very severe COPD, smoking history of ≥10 pack-years or biomass exposure	N=1,670 48 weeks	Primary: Number of COPD exacerbations per participant in 48 weeks, annualized as a rate per patient per year Secondary: Time to first severe exacerbation leading to hospitalization or death, health status using SGRQ and CAT scores and pre and post-	Primary: Annualized exacerbation rates across the three treatment arms were similar: 0.89 (95% CI, 0.77 to 1.02) on theophylline plus prednisone, 0.86 (95% CI, 0.75 to 0.99) on theophylline plus placebo and 1.00 (95% CI, 0.87 to 1.14) on placebo at week 48. There was no statistical difference in the rate ratio of exacerbations in the comparison between theophylline plus prednisone versus pooled theophylline plus placebo and placebo, which was 0.96 (95% CI, 0.83 to 1.12; P=0.6084). The rate ratio for theophylline plus placebo versus placebo was 0.87 (95% CI, 0.73 to 1.03; P=0.101) and for theophylline plus prednisone versus placebo was 0.90 (95% CI, 0.76 to 1.06; P=0.201). Secondary: Secondary outcomes of hospitalizations, FEV_1, SGRQ and COPD Assessment Test score showed no statistically significant difference between treatment arms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			bronchodilator FEV_1, FVC and FEV_1/FVC ratio.	
Lee et al.[46] (2009) Theophylline-containing drug regimens vs drug regimens not containing theophylline	RETRO Male patients aged 45 years or older with a diagnosis of COPD who received respiratory medications who were identified through the National Veterans Affairs inpatient, outpatient, pharmacy, and mortality databases	N=183,573 4 years	Primary: All-cause mortality, COPD Exacerbations, and COPD-related hospitalizations Secondary: Not reported	Primary: Overall, patients receiving a theophylline-containing regimen were found to have a small, but significant increased risk of death. The risk ranged from 1.11 to (95% CI, 1.04 to 1.18) for the combination of ipratropium plus theophylline to 1.31 (95% CI, 1.11 to 1.55) for ICS plus long acting β_2-agonist and theophylline. Theophylline regimens containing solely ipratropium or an ICS, or a combination of them both had significantly higher COPD exacerbations compared to similar therapy without theophylline. Theophylline was associated with an increased hospitalization rate for two regimens (ipratropium and ipratropium plus ICS). Secondary: Not reported
Lee et al.[47] (2008) Exposure to ICS, ipratropium, LABA, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.88). LABA (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Exercise-Induced Bronchospasm				
Furukawa et al.[48] (1983) Dyphylline 10 mg/kg administered 1 hour prior to exercise vs dyphylline 15 mg/kg administered	DB, PC, RCT, XO Patients between 12 and 17 years old with exercise-induced bronchospasm (≥20% decrease in FEV_1 during treadmill exercise test)	N=20 1 day	Primary: Spirometry, PEFR, physical examination, subjective symptoms Secondary: Not reported	Primary: After exercise, there was a mean reduction for placebo, theophylline, dyphylline 10 mg/kg, dyphylline 15 mg/kg, and dyphylline 20 mg/kg in FEV_1 (30.5, 8.8, 26.3, 23.5, and 21.5%, respectively). There was a significant difference in efficacy for preventing exercise-induced bronchospasm in patients receiving theophylline 6 mg/kg, dyphylline 15mg/kg, and dyphylline 20mg/kg compared to placebo (P<0.05). There was no statistically significant difference in blood pressure, pulse, hematologic, chemistry, or urine test among treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 hour prior to exercise vs dyphylline 20 mg/kg administered 1 hour prior to exercise vs theophylline 6 mg/kg administered 2 hours prior to exercise vs placebo				Not reported

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, IV=intravenous, QID=four times daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=crossover
Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, AUC=area under the curve, CI=confidence interval, COPD=chronic obstructive pulmonary disease, FEF=forced expiratory flow, FEV_1=forced expiratory volume in 1 second, FRC=functional residual capacity, FVC=forced vital capacity, ICS=inhaled corticosteroid, LABA=long-acting beta-2 agonist, OR=odds ratio, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, RR=relative risk, TGV=thoracic gas volume

Additional Evidence

Dose Simplification
Kelloway et al. analyzed pharmacy claims to assess adherence with theophylline and inhaled anti-inflammatory medications. Adherence was found to be better with theophylline than inhaled treatments (P=0.001).[49] Sherman et al. evaluated adherence rates with asthma medications in children with persistent asthma who were Medicaid recipients. Maximum potential adherence was 72% for theophylline, 61% for inhaled corticosteroids, and 38% for cromolyn. These findings indicate poor compliance with asthma therapy, especially evident with nebulized cromolyn. According to this study, physicians were only able to identify 50% of patients who were non-compliant with therapy, and approximately one third of patients who were excessively refilling their inhaled albuterol.[50]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Reed et al. evaluated health care resource utilization rates. Over a 12-month period, 1.3 to 4.7% of patients in the theophylline study group required ≥1 physician visit, emergency room department visit, or hospitalization compared to 1.2 to 4.1% for patients receiving beclomethasone. There was no significant difference between the treatment groups.[51] Tinkelman et al. also demonstrated comparable efficacy for theophylline and beclomethasone in decreasing physician visits and hospitalizations.[18] The available data demonstrates that aminophylline does not reduce the length of hospital stay during the acute management of asthma or COPD.[25-27,38,40]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Respiratory Smooth Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aminophylline	injection	N/A	N/A	$$
Theophylline	elixir*, extended-release capsule, extended-release tablet*, injection*, oral solution*	Theo-24®	$$$$$	$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The respiratory smooth muscle relaxants are approved for the treatment of asthma, chronic bronchitis and emphysema.[1-3] All of the products are available in a generic formulation.

For the treatment of asthma, guidelines recommend the use of low dose inhaled corticosteroid (ICS) as initial controller treatment. When additional therapy is needed, it is recommended that a long-acting β_2-agonist (LABA) be added to the regimen. Theophylline is considered an alternative treatment option for the management of asthma.[7,8] For the treatment of mild airflow obstruction associated with chronic obstructive pulmonary disease (COPD), guidelines recommend the use of a short-acting bronchodilator as needed to relieve breathlessness and exercise limitation. For patients who require daily maintenance therapy to control symptoms, an inhaled long-acting bronchodilator is recommended (β_2-agonist or antimuscarinic). Theophylline should only be used after a trial of inhaled bronchodilators or in patients who are unable to use inhaled therapy due to its potential toxicity.[4-6]

Numerous clinical trials have been conducted evaluating the efficacy and safety of the respiratory smooth muscle relaxants. While the majority of these trials have compared active treatment to placebo, or combination therapy to monotherapy, few studies have directly compared the xanthine derivatives. For the treatment of asthma and COPD, sustained-release theophylline has been shown to be either slightly less, or equally effective, when compared to ICS, inhaled LABAs, leukotriene modifiers, nedocromil, cromolyn, or ipratropium. The use of theophylline and aminophylline is often associated with a greater discontinuation rate due to adverse events than comparator drugs.[9-48] Trials comparing the various dosage forms of xanthines are limited; most dosage form comparison studies have evaluated pharmacokinetic data.[52-55]

Widespread use of the respiratory smooth muscle relaxants is limited by their narrow therapeutic index. Toxicity is a significant concern and close monitoring is essential. These agents must be carefully titrated according to therapeutic response and serum levels. Theophylline serum concentrations of 10 to 20 µg/mL are generally needed to produce bronchodilation. Serum levels >20 µg/mL are associated with unacceptable adverse events. The most common adverse events reported with theophylline include anorexia, nausea, vomiting, and headache. Cardiac arrhythmias, tachycardia, diarrhea, and seizures may occur with higher doses. A severe overdose with theophylline can be fatal.[1-4]

There is insufficient evidence to support that one brand respiratory smooth muscle relaxant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand respiratory smooth muscle relaxants within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand respiratory smooth muscle relaxant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Intranasal Corticosteroids
AHFS Class 520808
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I. Overview

Intranasal corticosteroids are primarily used to treat perennial and seasonal allergic rhinitis and may be useful in the treatment of some forms of nonallergic rhinitis.[1] Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing, and/or nasal itching. These symptoms result from a complex allergen driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators.[2] Intranasal corticosteroids downregulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes.[1]

Most intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of perennial and seasonal allergic rhinitis.[3-11] Mometasone carries an additional indication for the prophylaxis of seasonal allergic rhinitis.[8] Two currently available intranasal corticosteroids, beclomethasone (Beconase AQ®) and mometasone, are also FDA-approved for the management of nasal polyps.[3,11] Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction.[2] Two new dosage formulations have been approved for the treatment of nasal polyps in patients 18 years of age and older, Xhance® (fluticasone propionate nasal spray) and Sinuva® (mometasone furoate sinus implant).[7,9] Xhance® is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the device.[7] Sinuva® is to be inserted in the ethmoid sinus under endoscopic visualization by physicians trained in otolaryngology.[9]

Beclomethasone and fluticasone propionate are both approved for the management of nonallergic rhinitis (e.g., infectious rhinitis, hormonal rhinitis, and vasomotor nonallergic rhinitis with eosinophilia syndrome).[1,11] Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events.[14]

Beclomethasone (QNASL®) and ciclesonide (Zetonna®) were approved in 2012 and are the only two intranasal corticosteroid products formulated as a "dry" nasal aerosol; all other products in within the class are formulated as aqueous suspensions.[3-13] Mometasone is approved for use in children two years of age and older.[11] Dymista® (azelastine hydrochloride-fluticasone propionate) is a combination product that utilizes both an intranasal antihistamine and an intranasal corticosteroid to manage the symptoms of allergic rhinitis.[10]

The intranasal corticosteroids that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Flunisolide, fluticasone propionate, and mometasone are available in a generic formulation. This class was last reviewed inMay 2020.

Table 1. Intranasal Corticosteroids Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Beclomethasone	aerosol nasal spray, nasal spray	Beconase AQ®, QNASL®	none
Ciclesonide	aerosol nasal spray, nasal spray	Omnaris®, Zetonna®	Omnaris®, Zetonna®
Flunisolide	nasal spray	N/A	flunisolide
Fluticasone propionate	nasal spray*	Xhance®	fluticasone propionate
Mometasone	nasal implant, nasal spray*	Sinuva®	none
Combination Products			
Azelastine and fluticasone	nasal spray	Dymista®*	Dymista®*

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the intranasal corticosteroids are summarized in Table 2.

Table 2. Treatment Guidelines Using the Intranasal Corticosteroids

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)[2]**	Pharmacologic treatment of allergic rhinitis • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma & Immunology: **Allergic Rhinitis and its Impact on Asthma (ARIA)**	Should a combination of an oral H_1-antihistamine and intranasal corticosteroid vs intranasal corticosteroid alone be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an oral H_1-antihistamine or an intranasal corticosteroid alone is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid alone rather

Clinical Guideline	Recommendation(s)
guidelines-2016 revision (2016)[15]	than a combination of an intranasal corticosteroid with an oral H_1-antihistamine is suggested (very low certainty of evidence). • This recommendation concerns regular use of newer and less sedative oral H_1-antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis. For older oral H_1-antihistamines with more sedative effects, the balance of desirable and undesirable effects may be different. • Currently available evidence suggests that there is no additional benefit from a combination therapy compared with intranasal corticosteroid alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (very low certainty of evidence). • At initiation of treatment (approximately the first two weeks), a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine might act faster than an intranasal corticosteroid alone and thus might be preferred by some patients. The choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal H_1-antihistamine alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine rather than an intranasal H_1-antihistamine alone is suggested (low certainty of evidence). <u>Should a leukotriene receptor antagonist vs an oral H_1-antihistamine be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a leukotriene receptor antagonist or an oral H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an oral H_1-antihistamine rather than a leukotriene receptor antagonist is suggested (low certainty of evidence). • The choice of a leukotriene receptor antagonist or oral H_1-antihistamine will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an oral H_1-antihistamine might still be more cost-effective, but this will largely depend on availability of generic leukotriene receptor antagonists and the local cost of various newer-generation oral H_1-antihistamines and leukotriene receptor antagonists. • Some patients with allergic rhinitis who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from a leukotriene receptor antagonist more than from an oral H_1-antihistamine. However, this recommendation applies to treatment of allergic rhinitis but not to treatment of asthma. Patients with asthma who have concomitant allergic rhinitis should receive an appropriate treatment according to the guidelines for the treatment of asthma. <u>Should an intranasal H_1-antihistamine vs an intranasal corticosteroid be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (moderate certainty of evidence).

Clinical Guideline	Recommendation(s)
	• In patients with perennial allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (low certainty of evidence). Should an intranasal H_1-antihistamine vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (very low certainty of evidence). • The panel members acknowledged that the choice of treatment will depend mostly on patient preferences and local availability and cost of treatment.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[16]	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Oral antihistamines • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. Intranasal antihistamines • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin

Clinical Guideline	Recommendation(s)
	test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u>

Clinical Guideline	Recommendation(s)
	• A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. <u>Intranasal anticholinergics</u> • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. <u>Oral antileukotriene agents</u> • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. <u>Omalizumab</u> • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. <u>Nasal saline</u> • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. <u>Over-the-counter cough and cold medications for young children</u> • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Treatment of seasonal allergic rhinitis, an evidence-based focused 2017 guideline update**	<u>For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age:</u> • Routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine. • An intranasal corticosteroid is recommended over a leukotriene receptor antagonist (for ≥15 years of age). • For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.

Clinical Guideline	Recommendation(s)
(2017)[17]	
American Academy of Allergy, Asthma & Immunology: **Rhinitis 2020: A practice parameter update (2020)[18]**	• Prescribing first-generation antihistamines is not recommended; a second-generation antihistamine is preferred when prescribing an oral antihistamine for the treatment of AR. • Clinician should not select the oral LTRA montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies. • Clinicians should not select an oral LTRA for the treatment of NAR. • For the treatment of very severe or intractable AR, the clinician may consider a short course (5 to 7 days) of oral corticosteroids. • For the treatment of very severe or intractable AR, the clinician should not prescribe a depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects. • The clinician should offer intranasal antihistamine as an initial treatment option for patients with SAR. • The clinician should offer intranasal antihistamine as a first-line monotherapy option for patients with NAR. • The clinician should offer intranasal antihistamine as a first-line option for patients with intermittent AR. • When choosing monotherapy for persistent AR, intranasal corticosteroid should be the preferred medication. • For the initial treatment of moderate/severe SAR in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over an LTRA. • The use of intranasal decongestants should be short term and be used for intermittent or episodic therapy of nasal congestion. • In patients having severe mucosal edema, which impairs the delivery of other intranasal agents, an intranasal decongestant should be considered for up to five days of use. • Oral decongestant agents should be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome. • Oral decongestants should be avoided during the first trimester of pregnancy. • Patients with PAR and NAR who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium. • Intranasal cromolyn should be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures. • Clinicians should consider the combination of an intranasal corticosteroid and an internasal antihistamine for the initial treatment of moderate/severe nasal symptoms of SAR in patients age ≥12 years. • Clinicians should consider the combination of an intranasal corticosteroid and an intranasal antihistamine for moderate/severe SAR, PAR and NAR that is resistant to pharmacologic monotherapy. • For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium. • Patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to four weeks. • For patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician should consider the addition of pseudoephedrine, when tolerated. • For SAR, the clinician should not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine.

Clinical Guideline	Recommendation(s)
	• The clinician should not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients ≥12 years of age with symptoms of SAR. • Clinicians should not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR. • The addition of the oral LTRA montelukast to an intranasal corticosteroid for AR is not recommended. • Clinicians should offer an intranasal corticosteroid as a first-line therapy for NAR. • Clinicians should offer an intranasal antihistamine as a first-line therapy for NAR. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be offered through shared decision making to patients with moderate/severe AR who are not controlled with allergen avoidance and/or pharmacotherapy or choose immunotherapy as the preferred method of treatment and/or desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be considered for patients with controlled mild and moderate asthma with coexisting AR.
American Academy of Otolaryngology - Head and Neck Surgery Foundation: **Clinical Practice Guideline Allergic Rhinitis (2015)**[19]	• The clinical diagnosis of allergic rhinitis (AR) should be made when patients present with a history and physical exam consistent with an allergic cause and one or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. • Patients with a clinical diagnosis or AR who do not respond to empiric treatment, or in whom the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy, should have specific IgE (skin or blood) allergy testing. • Sinonasal imaging should not routinely be performed in patients presenting with symptoms consistent with a diagnosis or AR. • AR patients who have identified allergens that correlate with clinical symptoms may avoid known allergens or utilize environmental controls. • Patients with AR should be assessed for the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. • Intranasal steroids are recommended for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. • Oral second-generation/less-sedating antihistamines are recommended for patients with AR and primary complaints of sneezing and itching. • Intranasal antihistamines may be used in patients with seasonal, perennial, or episodic AR. • Oral leukotriene receptor antagonists should not be offered as primary therapy for patients with AR. • Combination pharmacologic therapy may be used in patients with AR who have inadequate response to pharmacologic monotherapy. Immunotherapy (sublingual or subcutaneous) should be offered to patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the intranasal corticosteroids are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Single Entity Intranasal Corticosteroids[3-13]

Indication	Beclomethasone	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
Allergic Rhinitis					
Prophylaxis of the nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age					✔ (suspension nasal spray)
Treatment of nasal congestion associated with seasonal allergic rhinitis in patients ≥2 years of age					✔ (suspension nasal spray)
Relief of the symptoms of seasonal or perennial allergic rhinitis	✔ (Beconase AQ®)		✔		
Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in patients four years of age and older	✔ (QNASL®)				
Treatment of nasal symptoms associated with seasonal allergic rhinitis in adults and children six years of age and older		✔ (Omnaris®)			
Treatment of perennial allergic rhinitis in adults and adolescents 12 years of age and older		✔			
Treatment of seasonal allergic rhinitis in adults and adolescents 12 years of age and older		✔ (Zetonna®)			
Treatment of symptoms of seasonal and perennial allergic rhinitis in adults and children ≥2 years					✔ (suspension nasal spray)
Management of nasal symptoms of seasonal and perennial allergic rhinitis in adults and pediatric patients 4 years of age and older				✔ (suspension nasal spray)	
Nasal Polyps					
Prevention of recurrence of nasal polyps following surgical removal	✔ (Beconase AQ®)				
Treatment of nasal polyps in patients ≥18 years of age				✔ (Xhance®)	✔ (suspension nasal spray)
Treatment of nasal polyps in patients ≥18 years of age who have had ethmoid sinus surgery					✔ (Sinuva®)
Nonallergic Rhinitis					
Relief of the symptoms of nonallergic rhinitis	✔				

Indication	Beclomethasone	Ciclesonide	Flunisolide	Fluticasone Propionate	Mometasone
	(Beconase AQ®)				
Management of the nasal symptoms of perennial nonallergic rhinitis in adults and pediatric patients four years of age and older				✔ (suspension nasal spray)	

Table 4. FDA-Approved Indications for the Combination Intranasal Corticosteroids[3-13]

Indication	Azelastine and Fluticasone
Relief of symptoms of seasonal allergic rhinitis in patients six years of age and older	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the intranasal corticosteroids are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Intranasal Corticosteroids[13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Beclomethasone	Not available	94 to 96	Hepatic and respiratory	Renal (<10) Feces (main, percent not specified)	2.8
Ciclesonide	<1	≥99	Hepatic predominantly, respiratory	Renal (<20) Feces (66)	6 to 7
Flunisolide	50	Not reported	Hepatic	Renal (65 to 70) Feces (percent not reported)	1 to 2
Fluticasone propionate	<2	91	Hepatic	Renal (<5) Feces (95)	3.2 to 11.2
Mometasone	Undetectable	98 to 99	Hepatic, extensive	Renal (8) Feces (74)	5.0 to 5.8
Combination Products					
Azelastine and fluticasone	A: 40 F: 0.5	A: not reported F: >99	A: Hepatic, extensive (percent not reported) F: Hepatic	A: Renal (25) Feces (50 to 75) F: Renal (2) Feces (90)	A: 22 to 25 F: 15.1

V. Drug Interactions

Major drug interactions with the intranasal corticosteroids are listed in Table 6.

Table 6. Major Drug Interactions with the Intranasal Corticosteroids[13]

Generic Name(s)	Interaction	Mechanism
Fluticasone	Human immunodeficiency virus (HIV)/ Hepatitis C virus protease Inhibitors	Plasma concentrations and pharmacologic effects of specific inhaled steroids may be increased by HIV protease inhibitors. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur. Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of specific inhaled steroids. Severe adrenal suppression and iatrogenic Cushing's syndrome may occur.
Fluticasone	Azole antifungals	Azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids (budesonide and fluticasone only) resulting in enhanced corticosteroid effects and toxicity.
Fluticasone	Cobicistat	Concurrent use of budesonide and cobicistat may result in increased budesonide plasma concentrations and increased risk for systemic corticosteroid effects.

VI. Adverse Drug Events

The most common adverse drug events reported with the intranasal corticosteroids are listed in Tables 7 and 8.

Table 7. Adverse Drug Events (%) Reported with the Single Entity Intranasal Corticosteroids[3-13]

Adverse Events	Beclomethasone	Ciclesonide	Flunisolide	Fluticasone Propionate	Fluticasone (Xhance®)	Mometasone	Mometasone (Sinuva®)
Cardiovascular							
Chest pain	-	-	-	-	-	2 to <5	-
Central Nervous System							
Dizziness	-	✔	-	1 to 3	✔	-	3.5
Headache	<5	6.0 to 6.6	≤5	6.6 to 16.1	3.7 to 5.0	26	-
Lightheadedness	<5	-	-	-	-	-	-
Gastrointestinal							
Abdominal pain	-	-	-	1 to 3	✔	-	-
Diarrhea	-	-	-	1 to 3	-	2 to <5	-
Dyspepsia	-	-	-	-	-	2 to <5	-
Nausea	<5	>2[†]	≤5	2.6 to 4.8	-	2 to <5	-
Vomiting	-	-	≤5	2.6 to 4.8	-	5	-
Hypersensitivity reactions							
Anaphylaxis	✔	-	-	✔	✔	✔	-
Angioedema	✔	-	-	✔	-	✔	-
Bronchospasm	✔	-	-	✔	-	-	-
Dyspnea	-	-	-	✔	-	-	-
Edema of face/ tongue	-	-	-	✔	-	-	-
Pruritus	-	-	-	✔	-	-	-
Rash	✔	-	-	✔	-	-	-
Wheezing	✔	-	-	✔	-	2 to <5	-
Urticaria	✔	-	-	✔	-	-	-
Ophthalmic							
Blurred vision	-	-	-	✔	-	-	-
Cataracts	✔	✔	-	✔	✔	✔	✔
Conjunctivitis	-	-	-	✔	-	2 to <5	-
Dry/irritated eyes	-	-	-	✔	-	-	-
Glaucoma	✔	✔	-	✔	✔	✔	✔
Increased intraocular pressure	5	-	-	✔	✔	-	-
Watery eyes	<3	-	≤5	-	-	-	-
Respiratory							
Asthma symptoms	-	-	-	3.3 to 7.2	-	2 to <5	4.7

Adverse Events	Beclomethasone	Ciclesonide	Flunisolide	Fluticasone Propionate	Fluticasone (Xhance®)	Mometasone	Mometasone (Sinuva®)
Bronchitis	-	≥2	-	1 to 3	-	2 to <5	2.0
Cough	-	≥2	>1	3.6 to 3.8	-	7	-
Epistaxis	<3	4.9 to 11.4†	3 to 9	6.0 to 6.9	9.9 to 11.9	1 to 13	2.4
Hoarseness	-	-	≤1	✔	-	-	-
Mild nasopharyngeal irritation	24*	-	-	-	-	-	-
Nasal burning/ stinging	-	-	13 to 45	2.4 to 3.2	-	✔	-
Nasal congestion	≤3	✔	-	-	4.4 to 5.6	-	-
Nasal discomfort	5.2†	3.2 to 5.7†	-	-	-	-	-
Nasal dryness	✔	-	>1	-	✔	-	-
Nasal irritation	✔	≥3	≤5	-	-	2 to <5	-
Nasal mucosal erythema	-	-	-	-	5.0 to 5.6	-	-
Nasal mucosal ulceration	✔	✔	≤1	✔	2.5 to 3.8	✔	-
Nasal septal perforation/ulceration	✔	✔	✔	✔	6.9 to 7.5	✔	✔
Nasal stuffiness/ congestion	<3	✔	≤5	-	-	-	-
Nasopharyngitis	-	3.7 to 6.6	-	-	1.9 to 7.5	-	1.2
Pharyngitis	-	<3.4	>1	6 to 7.8	1.3 to 3.1	12	-
Rhinitis	-	-	-	-	-	2 to <5	-
Rhinorrhea	<3	-	-	1 to 3	-	-	-
Sinusitis	-	≥3	≤1	-	4.4 to 5.0	5	-
Sneezing	4*	-	≤5	-	-	-	-
Streptococcal pharyngitis	-	>2†	-	-	-	-	-
Throat discomfort (burning, itching, swelling, pain)	-	-	≤5	✔	-	-	-
Throat dryness/ irritation	✔	-	-	✔	-	-	-
Upper respiratory tract infection	-	>2†	-	-	-	5 to 7	-
Voice changes	-	-	-	✔	-	-	-
Miscellaneous							
Aches and pains	-	-	-	1 to 3	-	-	-
Aftertaste	-	-	8 to 17	-	-	-	-
Arthralgia	-	-	-	-	-	2 to <5	-
Back pain	-	≥3	-	-	-	-	-
Dysmenorrhea	-	-	-	-	-	5	-
Earache	-	2.2	-	-	-	2 to <5	-
Fever	3	-	-	1 to 3	-	-	-
Flu-like symptoms	-	-	-	1 to 3	-	2 to <5	-
Growth suppression	✔	✔	✔	✔	✔	✔	-
Immunosuppression	-	✔	-	-	✔	✔	✔

Adverse Events	Beclomethasone	Ciclesonide	Flunisolide	Fluticasone Propionate	Fluticasone (Xhance®)	Mometasone	Mometasone (Sinuva®)
Impaired wound healing	-	✔	-	-	-	✔	-
Infection	✔	✔	✔	✔	-	✔	✔
Influenza	-	≥3	-	-	-	-	-
Loss of taste/smell	✔	-	✔	✔	-	-	-
Muscle strain	-	>2†	-	-	-	-	-
Myalgia	-	-	-	-	-	2 to <5	-
Otitis media	-	-	-	-	-	2 to <5	2.0
Skin trauma	-	-	-	-	-	2 to <5	-
Toothache	-	-	-	-	✔	-	-
Unpleasant taste/ smell	✔	-	-	-	-	✔	-
Urinary tract infection	-	≥3	-	-	-	-	-
Viral infection	-	-	-	-	-	14	-

✔ Percent not specified.
- Event not reported.
*Beconase AQ® only.
†Aerosol formulation only.

Table 8. Adverse Drug Events (%) Reported with the Combination Intranasal Corticosteroids[10-13]

Adverse Event(s)	Azelastine and Fluticasone
Central Nervous System	
Dizziness	-
Dysesthesia	-
Headache	≥2
Somnolence	-
Gastrointestinal	
Diarrhea	≥2
Nausea	-
Respiratory	
Asthma	-
Cold symptoms	-
Epistaxis	≥2
Nasal burning	-
Nasal congestion	≥2
Nasal discomfort	-
Nasal ulcers	-
Paroxysmal sneezing	-
Pharyngitis	≥2
Pharyngolaryngeal pain	-
Rhinitis	≥2
Sinusitis	-
Sneezing	-
Upper respiratory tract infection	≥2
Other	
Bitter taste	-
Conjunctivitis	-
Cough	≥2
Dry mouth	-
Dysgeusia	4
Fatigue	-
Pain	≥2
Pyrexia	≥2
Viral infection	≥2
Weight increase	-

- Event not reported or below the 2% reported frequency threshold.

VII. Dosing and Administration

The usual dosing regimens for the intranasal corticosteroids are listed in Table 9.

Table 9. Usual Dosing Regimens for the Intranasal Corticosteroids[3-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Beclomethasone	Nasal polyps, nonallergic (vasomotor) rhinitis: Suspension: one to two inhalations in each nostril BID Perennial allergic rhinitis, seasonal allergic rhinitis: Aerosol: two 80 µg inhalations in	Nasal polyps, nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis in children six to 12 years of age: Suspension: initial, one inhalation in each nostril BID; maximum, two inhalations in	Aerosol for nasal inhalation: 40 µg/actuation 80 µg/actuation (120 actuations) Suspension for nasal inhalation:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	each nostril QD Suspension: one to two inhalations in each nostril BID	each nostril BID Perennial allergic rhinitis, seasonal allergic rhinitis in children 4 to 11 years of age: Aerosol: one 40 µg inhalations in each nostril QD Perennial allergic rhinitis, seasonal allergic rhinitis in children ≥12 years of age: Aerosol: two 80 µg inhalations in each nostril QD Suspension: one to two inhalations in each nostril BID	42 µg/inhalation (180 metered doses)
Ciclesonide	Perennial allergic rhinitis, seasonal allergic rhinitis: Aerosol: one inhalation in each nostril QD Suspension: two inhalations in each nostril QD	Perennial allergic rhinitis, seasonal allergic rhinitis in children ≥12 years of age: Aerosol: one inhalation in each nostril QD Suspension: two inhalations in each nostril QD Seasonal allergic rhinitis in children six years of age and older: Suspension: two inhalations in each nostril QD	Aerosol for nasal inhalation: 37 µg/actuation (60 actuations) Suspension for nasal inhalation: 50 µg/inhalation (120 metered doses)
Flunisolide	Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril BID; maximum, eight inhalations in each nostril daily	Perennial allergic rhinitis, seasonal allergic rhinitis in children six to 14 years of age: Suspension: one inhalation in each nostril TID or two inhalations in each nostril BID; maximum, four inhalations in each nostril daily	Suspension for nasal inhalation: 25 µg/inhalation (200 metered doses)
Fluticasone propionate	Nasal polyps in adults ≥18 years of age: Exhaler suspension: one spray in each nostril twice daily Nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal rhinitis: Suspension: two inhalations in each nostril QD or one inhalation in each nostril BID; maintenance, one inhalation in each nostril QD	Nonallergic (vasomotor) rhinitis, perennial allergic rhinitis, seasonal rhinitis in children four years of age and older: Suspension: one inhalation in each nostril QD; maximum, two inhalations in each nostril QD	Suspension for nasal inhalation: 50 µg/inhalation (120 metered sprays) Exhaler suspension for nasal inhalation: 93 µg/inhalation (120 metered sprays)
Mometasone	Nasal congestion associated with seasonal allergic rhinitis: Suspension: two inhalations in each nostril QD	Nasal congestion associated with seasonal allergic rhinitis in children two to 11 years of age: Suspension: one inhalation in	Nasal implant: 1350 µg Suspension for nasal inhalation:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Nasal polyps in adults ≥18 years of age: Suspension: two inhalations in each nostril QD to BID Nasal polyps in adults ≥18 years of age who have had ethmoid sinus surgery: Nasal implant: one implant is loaded into a Delivery System and placed in the ethmoid sinus under endoscopic visualization; the implant may be left in the sinus up to 90 days and can be removed at day 90 or earlier at the physician's discretion Perennial allergic rhinitis, seasonal allergic rhinitis: Suspension: two inhalations in each nostril QD Prophylaxis of seasonal allergic rhinitis in individuals >12 years of age: Suspension: two inhalations in each nostril QD	each nostril QD Perennial allergic rhinitis, seasonal allergic rhinitis in children two to 11 years of age: Suspension: one inhalation in each nostril QD	50 µg/inhalation (120 metered doses)
Combination Products			
Azelastine and fluticasone	Seasonal allergic rhinitis: Suspension: one inhalation in each nostril BID	Seasonal allergic rhinitis in children ≥6 years of age: Suspension: one inhalation in each nostril BID	Suspension for nasal inhalation: 137-50 µg/inhalation

BID=twice daily, QD=once daily, BID=twice daily, TID=three times daily

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the intranasal corticosteroids are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Intranasal Corticosteroids

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Allergic Rhinitis (Perennial and Seasonal)				
Meltzer et al.[20] (2012) Beclomethasone 320 µg QD (QNASL®) vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with a ≥2 year history of PAR, a positive skin test to ≥1 perennial allergen	N=474 6 weeks	Primary: Change from baseline in rTNSS Secondary: Change from baseline in iTNSS, individual symptom scores, PNSS, RQLQ and safety	Primary: After six weeks of treatment, subjects treated with beclomethasone reported significantly greater improvement from baseline in rTNSS compared to subjects treated with placebo. (LS mean change of -2.46 vs -1.63; P<0.001). Secondary: A significantly greater improvement in iTNSS was achieved over six weeks in the beclomethasone treatment group compared to the placebo group (LS mean change of -2.14 vs -1.36; P<0.001). As demonstrated with overall nasal symptom improvement, beclomethasone significantly improved reflective and instantaneous individual nasal symptom scores for all four of the components of the TNSS compared to placebo (P<0.05 for all). The change from baseline in PNSS was significantly greater with beclomethasone compared to placebo over six weeks (P<0.001). Furthermore, patients treated with beclomethasone achieved significant improvements in all individual symptoms of the PNSS compared to subjects treated with placebo (P≤0.001 for all). Beclomethasone treatment significantly improved RQLQ scores compared to placebo (P=0.001). There were no differences between beclomethasone and placebo with regard to the incidence, type and severity of adverse events. Nasal discomfort was frequently reported with both beclomethasone and placebo treatment (5.9 and 5.0%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van Bavel et al.[21] (abstract) (2012) Beclomethasone 320 µg QD (QNASL®) vs placebo	DB, PC, RCT Patients ≥12 years of age with SAR	N=340 2 weeks	Primary: Changes in rTNSS, iTNSS, RQLQ score, rTOSS, iTOSS, PNSS scores and safety Secondary: Not reported	Primary: Patients treated with beclomethasone experienced a significantly greater improvement from baseline in average morning and evening rTNSS compared to treatment with placebo (treatment difference, -0.91; 95% CI, -1.3 to -0.5; P<0.001) over two weeks of treatment. Greater improvements in rTNSS with beclomethasone compared to placebo were evident by day two of treatment and were maintained throughout the treatment period. Similarly, beclomethasone treatment significantly improved iTNSS (P<0.001) and RQLQ score (P=0.005) compared to placebo. Treatment with beclomethasone was associated with greater improvements in rTOSS (P=0.002), iTOSS (P=0.003) and PNSS (P<0.001) compared to treatment with placebo. The overall safety profile was similar between patients treated with beclomethasone or placebo. Secondary: Not reported
Berger et al.[22] (2015) Beclomethasone 80 µg QD vs placebo	DB, PC, RCT Children aged four to 11 years with PAR	N=547 12 weeks	Primary: Change from baseline in average morning and evening rTNSS during the first six weeks of treatment in patients six to 11 years of age Secondary: Change from baseline in the average morning and evening iTNSS in six to 11 year olds and the change from baseline in average rTNSS and iTNSS in	Primary: Improvements in the average morning and evening rTNSS were significantly greater with once-daily treatment of beclomethasone nasal aerosol than with placebo (mean treatment difference −0.66; P=0.002). Secondary: Improvement in the average morning and evening iTNSS was significantly greater for patients treated with beclomethasone nasal aerosol than those treated with placebo during the first six weeks in children six to 11 years of age (mean treatment difference, −0.58; P=0.004). For children four to 11 years of age, improvements in the average rTNSS and average iTNSS were significantly greater for patients treated with beclomethasone nasal aerosol at 80 µg/day than those treated with placebo during the first six weeks of the study (mean treatment difference, −0.62; P=0.002; and −0.54; P=0.004,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			four to 11 year olds during the first six weeks of treatment	respectively). Similar results were observed for rTNSS and iTNSS during 12 weeks of treatment (mean treatment difference, −0.61; P=0.006; and −0.58; P=0.006, respectively, in children six to 11 years of age; and −0.53; P=0.009 and −0.52; P=0.008, respectively, in children four to 11 years of age).
Chervinsky et al.[23] (2007) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2 year history of PAR, who require continuous treatment and demonstrated skin prick test sensitivity to at least one allergen known to induce PAR	N=663 52 weeks	Primary: Treatment-emergent adverse events, 24 hour urinary free cortisol and morning cortisol levels at weeks 24 and 48 Secondary: Change from baseline in patient evaluated morning 24 hour rTNSS, PANS score at the end of treatment, combined RQLQ scores at end point	Primary: There were no clinically significant differences in the incidence of treatment-emergent adverse events with ciclesonide compared to placebo (75.1 vs 74.3%; P value not reported). No clinically significant differences were seen between the ciclesonide and placebo groups with regards to 24 hour urinary free cortisol and morning cortisol levels and ocular examinations. Secondary: There was a significantly greater reduction from baseline in 24 hour rTNSS in the ciclesonide group (-2.3) compared to placebo (-1.8) (P<0.001). No appreciable differences were found between ciclesonide and placebo groups in PANS score at the end of treatment. At the end point, ciclesonide produced a greater improvement in combined RQLQ scores compared to placebo (-1.07 vs -0.88; P=0.04).
Meltzer et al.[24] (2007) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, RCT Patients ≥12 years of age with a ≥2 year history of PAR, who required continuous or intermittent treatment and demonstrated skin prick test	N=676 6 weeks	Primary: Change from baseline in the average of morning and evening rTNSS Secondary: Average morning and evening patient evaluated iTNSS, PANS score at end of treatment, combined RQLQ score at the end	Primary: Ciclesonide significantly reduced average morning and evening rTNSS compared to placebo (-2.51 vs -1.89; P<0.001). Secondary: Ciclesonide significantly reduced average morning and evening iTNSS through six weeks of therapy (P=0.001). A greater decrease from baseline was observed at the end of treatment in PANS scores for the ciclesonide group compared to the placebo group (P=0.051). There was a significant improvement seen in the ciclesonide group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	sensitivity to ≥1 allergen known to induce PAR		of treatment	compared to placebo in combined RQLQ scores at the end of treatment (-1.30 vs -1.01; P=0.01).
Ratner et al.[25] (2006) Ciclesonide 200 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of SAR who require treatment and demonstrated skin prick test sensitivity to mountain cedar pollen	N=327 4 weeks	Primary: Change from baseline in average morning and evening rTNSS Secondary: Patient assessed iTNSS, PANS score at days 15 and 29, combined RQLQ scores at days 15 and 29, individual nasal symptoms, time to onset of effect and adverse events	Primary: Over two weeks, ciclesonide significantly improved the average morning and evening rTNSS compared to placebo (-2.40 vs -1.50; P<0.001). The change from baseline over the entire study period was significant for the ciclesonide group compared to placebo (P<0.001). Secondary: By two weeks, ciclesonide improved iTNSS compared to placebo (P<0.001). At day 15, treatment with ciclesonide provided significantly greater improvements in overall PANS and combined RQLQ scores compared to placebo (P≤0.002). By the end of the study, statistically significant differences were not seen between the ciclesonide and placebo groups (P value not reported). The ciclesonide group had a greater response in nonnasal symptom scores compared to placebo; however, this was not statistically significant (-1.73 vs -1.30; P=0.071). By day 15, treatment differences for nasal symptoms favoring ciclesonide were evident (P<0.001). Significant improvements in average morning and evening rTNSS with ciclesonide over placebo were seen by the second day of treatment (P<0.05). The frequency of adverse events was similar between the ciclesonide and placebo treatment groups (40.2 vs 39.3%, respectively; P value not reported). The most common adverse events for the ciclesonide group included nasal passage irritation (6.1%) and headache (5.5%).
Ratner et al.[26] (2010)	DB, MC, PC, PG, RCT	N=777 2 weeks	Primary: Change from baseline in rTNSS	Primary: The 80 and 160 µg treatment groups experienced a 15.1 and 16.0% reduction in rTNSS, respectively, compared to a 3.7% reduction for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ciclesonide 80 µg QD (Zetonna®) vs ciclesonide 160 µg QD (Zetonna®) vs placebo	Patients ≥12 years of age with SAR to for ≥2 years and a sensitivity to mountain cedar pollen through a standard skin prick test		Secondary: Change from baseline in iTNSS, rTOSS, iTOSS, individual symptom scores, RQLQ and safety	the placebo group (P<0.001 for both). Secondary: Patients randomized to receive 80 or 160 µg of ciclesonide experienced a 14.3 and 15.4% reduction, respectively, in iTNSS score compared to placebo (3.9%; P<0.001 for both). Both the 80 and 160 µg doses of ciclesonide were associated with statistically significant improvements in rTOSS compared to placebo (15.7 and 15.0 vs 6.8%, respectively; P<0.01). An improvement from baseline in iTOSS was also achieved with both 80 µg (P=0.008) and 160 µg (P=0.002) of ciclesonide compared to placebo. Furthermore, individual morning and evening reflective and instantaneous nasal symptom scores of nasal congestion, runny nose, sneezing, and nasal itching were significantly improved with 80 and 160 µg doses of ciclesonide compared to placebo (P<0.001 for both). Overall, both doses of ciclesonide were associated with statistically significant improvements in RQLQ scores from baseline compared to patients receiving placebo (P<0.001 for both). The incidence of adverse events was comparable between the ciclesonide treatment groups and placebo. The incidence of nasal erosions was 1.3% in the 80 µg treatment group and 0.9% in the 160 µg treatment groups. These erosions were assessed as mild in intensity and did not lead to discontinuation from the study.
Berger et al.[27] (abstract) (2012) Ciclesonide 74 µg QD (Zetonna®) vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of PAR	N=1,111 26 weeks	Primary: Change from baseline in rTNSS, iTNSS, RQLQ and treatment-related adverse events Secondary: Not reported	Primary: Patients receiving the 74 or 148 µg ciclesonide dose experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 0.65 and 0.52, respectively; P≤0.01 for both compared to placebo). The total scores for iTNSS were significantly improved with both the 74 and 148 µg ciclesonide doses compared to placebo (LS mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ciclesonide 148 µg QD (Zetonna®) vs placebo				change of 0.51 and 0.42, respectively; P<0.05). Both ciclesonide doses were associated with statistically significant improvements in RQLQ scores compared to placebo over 26 weeks (P<0.01). The overall incidence of adverse events was comparable between the treatment groups. Secondary: Not reported
Ratner et al.[28](abstract) (2012) Ciclesonide 74 µg QD (Zetonna®) vs ciclesonide 148 µg QD (Zetonna®) vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of SAR from mountain cedar pollen	N=671 2 weeks	Primary: Change from baseline rTNSS, iTNSS, rTOSS and safety Secondary: Not reported	Primary: Patients randomized to either the 74 or 148 µg ciclesonide doses experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 1.04 and 1.02, respectively; P≤0.01 for both compared to placebo). Patients who received either the 74 or 148 µg ciclesonide dose experienced significant improvements in iTNSS from baseline compared to the placebo group (LS mean change of 0.90 and 0.83 respectively; P<0.001 for both compared to placebo). Only the 74 µg ciclesonide treatment group experienced a statistically significant improvement in rTOSS compared to placebo (LS mean change of 0.52; P=0.0124). The overall incidence of adverse events was low and comparable between the treatment groups. Secondary: Not reported
Mohar et al.[29] (abstract) (2012) Ciclesonide 74 µg	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-	N=1,111 26 weeks	Primary: Change from baseline to six weeks in rTNSS, iTNSS, RQLQ scores and adverse events	Primary: Patients randomized to either the 74 or 148 µg ciclesonide doses experienced a statistically significant improvement from baseline in rTNSS compared to placebo (LS mean change of 0.70 and 0.54, respectively; P≤0.01 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD (Zetonna®) vs ciclesonide 148 µg QD (Zetonna®) vs placebo	year history of PAR		Secondary: Not reported	After six weeks of treatment, total iTNSS scores were significantly improved in both the 74 or 148 µg ciclesonide treatment groups compared to placebo (LS mean change of 0.58 and 0.42, respectively; P<0.05 for both). Six weeks of treatment with either dose of ciclesonide was associated with statistically significant improvements in RQLQ scores compared to placebo (P<0.01 for both). The overall incidence of adverse events was similar between the ciclesonide treatment groups and placebo over 26 weeks. Secondary: Not reported
LaForce et al.[30] (2009) Ciclesonide 300 µg QD (Zetonna®) vs ciclesonide 150 µg QD (Zetonna®) vs ciclesonide 75 µg QD (Zetonna®) vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR for ≥2 years and a sensitivity to grass or tree pollen via skin prick	N=513 2 weeks	Primary: Change from baseline in rTNSS Secondary: Change from baseline in iTNSS, morning iTNSS, RQLQ, rNNSS, PNSS and safety	Primary: The change from baseline in rTNSS was 0.81 (95% CI, 0.32 to 1.29; P=0.001), 0.90 (95% CI, 0.40 to 1.39; P<0.001) and 0.66 (95% CI, 0.16 to 1.16; P=0.01) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo. Secondary: All ciclesonide doses significantly improved the average morning and evening iTNSS during the study period compared to placebo. Treatment differences were 0.75 (95% CI, 0.26 to 1.23; P=0.002), 0.86 (95% CI, 0.36 to 1.35; P=0.001) and 0.75 (95% CI, 0.25 to 1.25; P=0.003) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo. Treatment differences for the reduction in the morning iTNSS were 0.86 (95% CI, 0.36 to 1.35; P<0.001), 1.03 (95% CI, 0.52 to 1.53; P<0.001) and 0.88 (95% CI, 0.37 to 1.39; P<0.001) for the ciclesonide 300, 150 and 75 µg groups, respectively, compared to placebo. Statistically significant improvements in RQLQ scores occurred with ciclesonide 300 µg (0.54; 95% CI, 0.10 to 0.98; P=0.02) and 75 µg (0.61; 95% CI, 0.16 to 1.06; P=0.008) compared to placebo, but not for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the 150 µg treatment group (0.38; 95% CI, -0.06 to 0.81; P=0.09). Significant improvements in PNSS scores occurred with ciclesonide 300 µg (0.91; 95% CI, 0.25 to 1.58; P=0.007), 150 µg (0.73; 95% CI, 0.05 to 1.40; P=0.04) and 75 µg (0.94; 95% CI, 0.25 to 1.62; P=0.007) compared to placebo. No differences in the type or severity of adverse events were reported between treatment groups. The most frequently reported adverse events were headache and nasal discomfort.
Ratner et al.[31] (2006) Ciclesonide 25 µg QD vs ciclesonide 50 µg QD vs ciclesonide 100 µg QD vs ciclesonide 200 µg QD vs placebo	DB, MC, PC, PG, Phase II, RCT Adult patients 18 to 65 years of age with a ≥2-year history of SAR, experiencing nasal allergy symptoms,	N=726 2 weeks	Primary: Change from baseline in sum of morning and evening rTNSS Secondary: Change from baseline in the sum of morning and evening iTNSS and use of rescue medications	Primary: Ciclesonide 100 and 200 µg, significantly improved the sum of morning and evening rTNSS compared to placebo (P=0.04 and P=0.003). The average change from baseline in rTNSS was -4.2 for placebo and -4.8, -4.8, -5.3 and -5.8 for ciclesonide 25, 50, 100 and 200 µg, respectively. Secondary: Both ciclesonide 100 and 200 µg demonstrated greater improvements in iTNSS compared to placebo (P value not reported). There were no appreciable differences in the use of rescue medication, chlorpheniramine, across all treatment groups.
Fokkens et al.[32] (2007)	DB, MC, PC, PG, RCT	N=285 2 weeks	Primary: Mean change from baseline over the entire	Primary: The mean change from baseline in daily rTNSS over the treatment period was greater for fluticasone furoate as compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 110 µg QD vs placebo	Patients ≥12 years of age with SAR, and either a positive skin prick test to grass pollen or a positive in vitro test for specific IgE, within 12 months prior to the study		treatment period in daily rTNSS Secondary: Mean change from baseline over the entire treatment period in daily rTOSS, morning predose iTNSS, overall evaluation of response to therapy, mean change from baseline in RQLQ, iTOSS, daily reflective and instantaneous individual symptom scores, time to onset of action	(-4.94 vs -3.18; P<0.001). Secondary: Fluticasone furoate was significantly more effective than placebo in improving daily rTOSS (-3.00 vs -2.26; P<0.001) as well as in improving morning predose iTNSS (-4.50 vs -2.60; P<0.001). In terms of overall response to therapy, 67% of patients receiving fluticasone furoate reported significant or moderate improvement, compared to 39% of patients given placebo (P<0.001). Overall RQLQ core decreased by 2.23 points in the fluticasone furoate group and by 1.53 points in the placebo group (P<0.001).
Gradman et al.[33] (2007) Fluticasone furoate 110 µg QD vs placebo	DB, NI, PC, RCT, XO Prepubertal children (6 to 11 years of age) with a diagnosis of PAR or SAR for ≥1 year, and either a positive skin prick test or a positive test for the specific IgE to an appropriate seasonal or perennial allergen	N=58 2 weeks	Primary: Mean growth rate in lower-leg length Secondary: Adverse events	Primary: A prespecified cutoff of no more than -0.20 mm/week was determined to be NI. The treatment difference in adjusted mean lower-leg growth rate between fluticasone furoate and placebo was -0.016 mm/week (95% CI, -0.13 to 0.10) demonstrating NI. Secondary: Reported adverse events were similar between the two groups.
Kaiser et al.[34] (2007)	DB, PC, PG, RCT Patients ≥12 years	N=299 2 weeks	Primary: Mean change from baseline over the entire	Primary: Fluticasone furoate significantly reduced nasal symptoms compared to placebo, with a treatment difference of -1.473 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 110 µg QD vs placebo	of age with SAR caused by ragweed pollen, with seasonal allergy symptoms during each of the past two fall allergy seasons; positive skin prick test response to ragweed allergen within 12 months prior to start of study		treatment period in daily rTNSS Secondary: Mean change from baseline over the entire treatment period in daily rTOSS, morning predose iTNSS, overall evaluation of response to therapy, HRQL based on RQLQ	 Secondary: An observed difference of -0.600 (P=0.004) favoring fluticasone furoate over placebo was recorded for the mean change from baseline in daily rTOSS over the entire treatment period. Fluticasone furoate demonstrated a significant reduction in morning predose iTNSS of -1.375 compared to placebo (P<0.001). A total of 73% of patients receiving fluticasone furoate compared to 52% of placebo-treated patients reported improvement in their overall evaluation of response to therapy (P<0.01). Fluticasone furoate-treated patients reported significant improvements in the overall RQLQ score compared to patients in the placebo group (-0.606; P<0.001). Adverse events occurred in 21% of patients receiving fluticasone furoate and 12% of patients that received placebo. The most common adverse event was headache (>3%), which was seen more often with fluticasone furoate than placebo; epistaxis was also commonly reported.
Nathan et al.[35] (2008) Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with PAR and a positive result to a skin prick test within 12 months of study entry or at study entry	N=455 4 weeks	Primary: Change from baseline in daily rTNSS Secondary: Change from baseline in AM predose iTNSS, AM and PM rTNSS, individual nasal symptoms, ocular symptoms, itching, QoL and response to therapy	Primary: The LS mean change from baseline during the treatment period in daily rTNSS was significantly greater in fluticasone furoate-treated patients compared to patients receiving placebo (treatment difference, -0.706; P=0.005). Secondary: The LS mean change from baseline in AM predose iTNSS during the entire treatment period was significantly greater in the fluticasone furoate treatment group compared to placebo (treatment difference, -0.705; P=0.006). Patients treated with fluticasone furoate experienced a significantly greater mean reduction in morning rTNSS (P=0.004) and evening rTNSS (P=0.011) compared to patients randomized to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The changes from baseline in AM and PM rTNSS scores for rhinorrhea, sneezing and nasal itching were significantly greater with fluticasone furoate treatment compared to placebo (P≤0.05 for all). There was no difference between treatments with regard to ocular symptoms. A significantly higher percentage of patients treated with fluticasone furoate reported treatment to be effective compared to patients receiving placebo (P=0.005).
Okubo et al.[36] (2014) Fluticasone furoate 55 µg QD vs placebo	DB, MC, PC, RCT Japanese patients aged 6 to <15 years with a history of PAR for one year or more, and positive for both a specific IgE antibody test to a PAR allergen (house dust mite or house dust) and nasal eosinophil counts, and with the three TNSS of 4 to <8 at baseline	N=261 2 weeks	Primary: Mean change from baseline in 3TNSS Secondary: 3 TNSS, 4 TNSS, TOSS, overall evaluation of response to therapy	Primary: The 3TNSS was greater for fluticasone furoate (-1.98) than for placebo (-0.89), and the difference (-1.089) was significant (P<0.001). Secondary: A significant treatment difference in mean change from baseline for 3TNSS was first observed on day 2 (P<0.001) for treatment compared with placebo. Treatment significantly improved all four individual nasal symptoms assessed and the 4TNSS compared with placebo in terms of the LS mean change from baseline in Weeks 1, 2, and over the entire treatment period. TOSS was reduced significantly in the treatment group compared with placebo in the second week and reduced numerically but not significantly in the first week. A significantly greater decrease in the mean change from baseline over the entire treatment period with respect to the score for troubles with daily life was observed in the treatment group compared with placebo (LS mean difference: -0.302; 95% CI, -0.42 to -0.19; P<0.001). A greater percentage of patients receiving fluticasone furoate (parent/guardian/patient: 21%, investigator: 24%) rated the overall response to therapy as “significantly improved” compared with patients receiving placebo (parent/guardian/patient: 2%, investigator: 9%). Adverse events reported during the study were of mild or moderate intensity and of similar type and frequency across the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Meltzer et al.[37] (2009) Fluticasone furoate 110 µg QD vs fluticasone furoate 55 µg QD vs placebo	DB, MD, PC, PG, RCT Patients 2 to 11 years of age with symptoms of SAR in the previous allergy season with a positive skin prick test for a specific IgE within previous 12 months	N=554 2 weeks	Primary: Change from baseline in daily rTNSS Secondary: Change from baseline in AM predose iTNSS, response to therapy, adverse events, laboratory tests, nasal examinations, vital signs and ECG	Primary: The change from baseline during the treatment period in daily rTNSS was significantly greater in the fluticasone furoate 110 µg treatment group compared to placebo (-3.16 vs -2.54; P=0.025). Patients receiving the 55 µg dose of fluticasone furoate experienced a numerically greater reduction in daily rTNSS compare to placebo (-2.71 vs -2.54), although this was not statistically significant (P=0.553). Secondary: The mean change in AM predose iTNSS was significantly greater for fluticasone furoate 110 µg compared to placebo (-2.80 vs -2.13; P=0.015), but not for the 55 µg fluticasone furoate dose (P value not reported). The overall response to therapy was significantly higher for the fluticasone furoate 110 µg treatment group compared to placebo (P<0.001), but not for the fluticasone furoate 55 µg treatment group compared to placebo (P=0.083). Adverse events were similar among treatment groups; however, the incidence was higher with the fluticasone 110 and 55 µg doses compared to placebo (30 vs 20%; P value not reported). There were no differences in laboratory tests or vital signs between the three treatment groups. The findings from nasal examinations and ECGs were similar between the treatment groups.
Maspero et al.[38] (2008) Fluticasone furoate 110 µg QD vs fluticasone	DB, MC, PC, PG, RCT Pediatric patients 2 to 11 years of age with a ≥6 month history PAR documented by a positive skin prick test against	N=558 12 weeks	Primary: Mean change from baseline in daily rTNSS over four weeks Secondary: Mean change from baseline in daily iTNSS, overall response to therapy and	Primary: Improvements in daily rTNSS over four weeks were not statistically significant compared to placebo for the fluticasone furoate 110 µg group (-0.452; P=0.073). Patients treated with fluticasone furoate 55 µg had statistically significant improvements in daily rTNSS compared to placebo (-0.754; P=0.003). Secondary: Both fluticasone furoate 55 (-0.751) and 110 µg (-0.651) demonstrated significant improvements from baseline in daily iTNSS compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
furoate 55 µg QD vs placebo	an appropriate perennial allergen		safety	placebo (P=0.002 and P=0.009). Treatment differences, determined by overall response to therapy, were not significant for patients in the fluticasone furoate 110 µg group compared to placebo (P=0.414) but were significant for the fluticasone furoate 55 µg group (P=0.024). Treatment with both doses of fluticasone furoate was well-tolerated over the 12-week period. Nasal examinations were similar across all three treatment groups and ophthalmic examinations revealed no differences between groups in terms of mean change from baseline intraocular pressure in each eye. Treatment differences for mean change from baseline in 24 hour urinary cortisol excretion from placebo at either dose of fluticasone furoate were not statistically significant (P value not reported).
Martin et al.[39] (2007) Fluticasone furoate 55 µg QD vs fluticasone furoate 110 µg QD vs fluticasone furoate 220 µg QD vs fluticasone furoate 440 µg	DB, PC, PG, RCT Patients ≥12 years of age with SAR during the past 2 mountain cedar allergy seasons and a positive skin test to mountain cedar allergy	N=642 14 days	Primary: Mean change from baseline in daily rTNSS Secondary: Mean change from baseline in morning predose iTNSS, mean change from baseline in daily rTOSS and iTOSS, mean change from baseline in morning and evening rTNSS and iTNSS and overall response to therapy	Primary: Fluticasone furoate 55, 110, 220 and 440 µg demonstrated statistically significant improvements with respect to the mean change from baseline in daily rTNSS compared to placebo (P<0.001 for all). Secondary: Fluticasone furoate was significantly more effective than placebo for mean changes from baseline in morning predose iTNSS (P<0.001 each dose vs placebo), daily rTOSS (P≤0.013 each dose vs placebo), and iTOSS (P≤0.019 for all). Over the entire treatment period, all doses of fluticasone furoate demonstrated significantly greater efficacy compared to placebo with regards to morning and evening rTNSS and iTNSS scores (P<0.001 for all). At the end of the treatment period, patients treated with fluticasone furoate rated their overall response to therapy significantly better than those treated with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD vs placebo				
Rosenblut et al.[40] (2007) Fluticasone furoate 110 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-history of PAR and a positive skin-prick test to an appropriate allergen either within the last 12 months prior to or at screening	N=806 12 months	Primary: Safety and tolerability based on adverse event data graded by severity (mild, moderate, or severe) as well as through the use of 24-hour urine samples, ECG, other laboratory measures and eye examinations Secondary: Not reported	Primary: Adverse events occurred in 77% of fluticasone furoate-treated patients and 71% of patients receiving placebo, where most were mild to moderate in intensity. The most frequently reported adverse events were headache and nasopharyngitis. Epistaxis was more frequently reported with patients treated with fluticasone furoate. There was no evidence of clinically relevant systemic corticosteroid exposure or impairment of HPA-axis function. Fluticasone furoate-treated patients had similar 24-hour urine cortisol results to those receiving placebo. There were no clinically meaningful differences between the groups in terms of other safety assessments, including mean changes in ophthalmic parameters. Secondary: Not reported
Vasar et al.[41] (2008) Fluticasone furoate 110 µg QD vs placebo	DB, PC, PG, RCT Patients ≥12 years of age with a history of PAR for ≥2 years and a positive skin-prick test to an appropriate perennial allergen	N=302 6 weeks	Primary: Mean change from baseline in rTNSS Secondary: Mean change from baseline in morning predose iTNSS, daily rTNSS, daily PNIF, and RQLQ scores, overall response to therapy and safety	Primary: The mean change from baseline in rTNSS was significantly greater in the fluticasone furoate group compared to placebo (-3.95 vs -2.69; P<0.001). Secondary: The mean change from baseline in morning predose iTNSS was significantly greater in fluticasone furoate patients compared to placebo (-3.82 vs -2.36; P<0.001). Treatment with fluticasone furoate demonstrated significantly greater efficacy compared to placebo in terms of improvements in daily iTNSS (P=0.004), PNIF (P=0.004) and overall RQLQ scores (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Thirty seven percent of patients treated with fluticasone furoate rated their overall response to therapy as "significantly improved" compared to 14% of patients treated with placebo (P<0.001). Treatment was well tolerated over the six week period.
Prenner et al.[42] (2010) Mometasone 100 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with SAR for ≥2 years, a positive skin prick test response and clinically symptomatic at screening	N=429 15 days	Primary: Change from baseline in iTOSS and iTNSS Secondary: Change from baseline in daily rTOSS and rTNSS, instantaneous nasal congestions scores, RQLQ, change from baseline in instantaneous and reflective individual symptom scores, subject and investigator evaluations of overall condition and therapeutic response	Primary: A significant reduction in iTOSS was observed in the mometasone group compared to placebo (P=0.026). A reduction in iTNSS was observed in the mometasone group compared to placebo (P<0.001). Secondary: A significant reduction in the LS mean change from baseline in rTOSS was observed in the mometasone group compared to placebo (P=0.005). A significant reduction in the LS mean change from baseline in rTNSS was observed in the mometasone group compared to placebo (P<0.001). A significant improvement in instantaneous ocular symptoms of itching/burning and watering/tearing was observed in the mometasone group compared to placebo (P<0.05). No significant difference was observed in the instantaneous eye redness score. A significant improvement in individual reflective ocular symptom scores was observed in the mometasone group compared to placebo (P<0.05). A significant improvement in all individual instantaneous and reflective nasal symptoms scores was observed in the mometasone group compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Greater improvements in overall SAR condition from baseline were observed in the mometasone group compared to placebo as rated by investigators and subjects (P<0.001 for both). Greater improvements in the RQLQ were observed in the mometasone group compared to placebo (P<0.001). The mometasone group showed a significantly greater response to therapy compared to the placebo group as rated by both investigators and subjects (P<0.001).
Makihara et al.[43] (2012) Mometasone 200 µg QD vs placebo	DB, PC, PG, RCT Patients 16 to 65 years of age with a ≥2 year history of Japanese cedar/cypress pollinosis sensitivity assessed by skin price	N=50 12 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline in TOSS, T5SS, QoL, daytime sleepiness, smell disturbances, frequency of rescue medication use, ECP levels in nasal secretions and safety	Primary: Compared to the placebo group, TNSS scores were significantly lower in the mometasone treatment group following 12 weeks of treatment (P<0.05). Secondary: After 12 weeks of treatment, there was no statistically significant difference between the mometasone and placebo treatment groups with regard to TOSS (P=NS). Compared to placebo, mometasone was associated with a statistically significant reduction in T5SS at 12 weeks (P<0.05). A statistically significant improvement in QoL occurred with mometasone compared to placebo at weeks two through 10 (P<0.05); however, the difference was not significant at week 12. There was no statistically significant difference between mometasone and placebo with regard to daytime sleepiness and smell disturbances at 12 weeks (P>0.05). No difference in rescue medication use with loratadine was reported between the treatment groups (P>0.05). At 12 weeks, there was no statistically significant difference between treatment groups with regard to nasal secretion levels of ECP (P=0.063).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in the rate of adverse events between the treatments. There were no patients that discontinued the study medication due to adverse events.
Baena-Cagnani et al.[44] (2010) Mometasone 100 µg QD vs placebo	DB, MC, PC, PG, RCT Patients 3 to 11 years of age with ≥1 year history of PAR requiring over-the-counter or prescription treatment and a positive skin prick test to one clinically significant perennial allergen	N=381 4 week efficacy phase followed by 6 month OL safety period	Primary: Change from baseline to day 15 in physician assessed TNSS Secondary: Change from baseline to day 15 in subject assessed TNSS, TSS, TNNSS, individual symptom scores and condition of PAR between baseline and endpoint	Primary: Patients randomized to mometasone experienced a significantly greater reduction in physician-assessed change in TNSS at day 15 compared to patients receiving placebo (-2.8 [-39%] vs -2.2 [-32%]; P=0.02). The changes in TNSS were also significant in favor of mometasone at days eight and 29 (P≤0.02 for both). Secondary: A significantly greater improvement in subject-assessed TNSS scores at day 15 occurred with mometasone compared to placebo (-1.7 [-28%] vs -1.1 [-18%]; P≤0.01). Mometasone treatment was associated with lower subject-assessed TSS scores at day 15 compared to placebo (-2.1 [-27%] vs -1.4 [-16%]; P<0.001). At day 15, subject assessed TNNSS scores were not significantly different between the treatment groups. Subject evaluations of all individual nasal symptom scores showed significantly greater improvement with mometasone compared to placebo over the first 15 days (P≤0.03 for all). Physician evaluation of the patients' condition favored mometasone treatment over placebo at both day 15 (P<0.01) and 29 (P=0.02).
Weinstein et al.[45] (2009) Triamcinolone 110 µg, 1 spray per nostril QD vs	DB, MC, PG, RCT Patients 2 to 5 years of age with at least 1 year history of PAR	N=474 28 days	Primary: Change from baseline in the mean daily instantaneous TNSS and change in individual treatment scores	Primary: Adjusted mean change for instantaneous TNSS was -2.28 for triamcinolone and -1.92 for the placebo group (P=0.09). The individual symptom score showed a significantly greater reduction with triamcinolone than placebo (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Change from baseline in the mean daily reflective TNSS	There was a significantly greater reduction in reflective TNSS from baseline in the triamcinolone group (-2.31) than the placebo group (1.87; P=0.03).
Svendsen et al.[46] (1989) Beclomethasone vs flunisolide	DB, RCT, XO Patients with PAR	N=23 8 weeks	Primary: Rhinitis symptoms and patient preference Secondary: Not reported	Primary: There were no statistically significant differences in rhinitis symptoms or patient preference between treatments (P value not reported). Secondary: Not reported
Al-Mohaimeid et al.[47] (1993) Budesonide 200 µg BID vs beclomethasone 200 µg BID	RCT, SB Patients 18 to 70 years of age with PAR	N=120 3 weeks	Primary: Nasal symptoms Secondary: Not reported	Primary: There were significantly fewer reports of sneezing with budesonide compared to beclomethasone (P=0.04). No statistically significant differences in symptoms of blocked nose, runny nose, itchy nose, runny eyes and sore eyes were reported (P>0.05). After three weeks of treatment, more patients reported being free of symptoms with budesonide compared to beclomethasone (38 vs 27%; P value not reported). More patients reported the treatment as noticeably, very, or totally effective with budesonide than with beclomethasone (72 vs 58%; P value not reported). Secondary: Not reported
McArthur et al.[48] (1994) Budesonide 200 µg BID vs	DB, RCT Adults with SAR	N=88 3 weeks	Primary: Nasal and non-nasal symptom score Secondary: Adverse events	Primary: Budesonide treatment resulted in significantly lower scores for runny nose, itchy nose and sneezing compared to beclomethasone at all time points (P<0.05), but the greatest difference occurred at the end of the treatment period. There was no statistically significant difference between treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
beclomethasone 200 µg BID				groups in scores for nasal blockage, runny eyes, and sore eyes (P value not reported). Secondary: Adverse events for both treatments were mild and transient.
Vanzieleghem et al.[49] (1987) Budesonide as needed, up to 2 sprays of 50 µg/spray in each nostril QID vs beclomethasone as needed, up to 2 sprays of 50 µg/spray in each nostril QID	DB, DD, RCT Patients with SAR during the ragweed-pollen season	N=61 7 weeks	Primary: Nasal symptoms, use of chlorpheniramine as rescue medication Secondary: Adverse events	Primary: Less budesonide was administered by the subjects than beclomethasone to maintain good control of nasal symptoms (P=0.016). No statistically significant difference was observed between treatment groups in the amount of oral chlorpheniramine used as rescue medication (P=NS). Secondary: Reported adverse events with both treatments were mild and transient.
Andersson et al.[50] (1995) Budesonide 200 or 400 µg QD vs fluticasone propionate 200 µg QD vs placebo	MC, PC, PG, RCT Patients with PAR	N=98 6 weeks	Primary: Rhinitis symptoms, use of terfenadine as rescue medication Secondary: Safety as assessed by rhinoscopy, urine cortisol and adverse events	Primary: There were no significant differences in nasal symptoms or eye symptoms between active treatment groups (P value not reported). All active treatments reduced terfenadine use compared to baseline, but this was significant with budesonide only (P<0.05). Secondary: Reported adverse events were few and minor. No significant differences in adverse events or 24-hour cortisol levels were reported between treatment groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Day et al.[51] (1998) Budesonide 256 µg QD vs fluticasone propionate 200 µg QD	DB, MC, PC, PG, RCT Patients ≥18 years of age with ≥1 year history of PAR and positive skin test to one or more perennial allergens	N=273 6 weeks	Primary: Nasal symptoms, patients' overall evaluation of efficacy and use of rescue medication Secondary: Adverse events	Primary: Both treatments resulted in significantly greater improvement in combined nasal symptom scores, runny nose and sneezing from baseline compared to placebo (P≤0.0012). Budesonide showed greater improvement in combined nasal symptom scores (P=0.031) and nasal blockage (P value not reported) than fluticasone propionate, but no statistically significant differences in runny nose or sneezing symptoms were detected (P value not reported). Significant improvements in nasal symptoms were seen at 36 hours with budesonide and 60 hours with fluticasone propionate (P value not reported). At six weeks of treatment, there were no statistically significant differences in patients' overall evaluation of efficacy (P=0.44) or use of antihistamines as rescue medication (no P values reported) between treatment groups. Secondary: The rates of reported adverse events were 46% with budesonide, 37% with fluticasone propionate and 36% with placebo (P values not reported). No signs of fungal infection were detected in the study population.
Shah et al.[52] (2003) <u>Study 1:</u> Budesonide 32 µg in each nostril for one dose vs fluticasone propionate 100 µg in each nostril for one dose	MC, RCT, SB, XO Patients ≥18 years of age with ≥1year history of allergic rhinitis and experiencing mild to moderate symptoms	N=181 (Study 1) N=190 (Study 2) 1 day	Primary: Sensory Perceptions Questionnaire and patients' product preference Secondary: Adverse events	Primary: In study one, significantly fewer patients perceived the scent (P<0.001), taste (P<0.001), aftertaste (P<0.001), throat rundown (P<0.001), and nose run out (P<0.019) with budesonide than with fluticasone propionate. In study two, significantly fewer patients detected an altered scent or taste with budesonide compared to fluticasone propionate (P<0.001). There were no significant differences between budesonide and fluticasone propionate in aftertaste, throat rundown, and nose run out. More patients perceived the spray in the throat as less wet (P<0.004 for study one and P<0.002 for study two) and therefore preferred the feel of the spray in the throat (P<0.001 for both studies) of budesonide to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<u>Study 2:</u> Budesonide 32 µg in each nostril for one dose vs fluticasone propionate 50 µg in each nostril for one dose				that of fluticasone propionate. More patients perceived the spray in the nose as less wet (P<0.001 for both studies) and therefore preferred the feel of the spray in the nose (P<0.001 for both studies) of budesonide to fluticasone propionate. Significantly more patients perceived a less forceful spray with budesonide and therefore preferred budesonide to fluticasone propionate (P<0.001). Overall, significantly more patients preferred budesonide compared to fluticasone propionate (P=0.02). Secondary: Budesonide and fluticasone propionate were both well tolerated.
Stern et al.[53] (1997) Budesonide 128 µg or 256 µg QD vs fluticasone propionate 200 µg QD vs placebo	MC, PC, PG, RCT Patients 18 to 72 years of age, with ≥2-year history of allergic rhinitis	N=635 4 to 6 weeks	Primary: Nasal and eye symptoms Secondary: Adverse events	Primary: Budesonide and fluticasone propionate treatment resulted in significant improvements in individual nasal symptoms such as blocked nose, runny nose, sneezing (P<0.001), combined nasal symptoms (P<0.001), eye symptoms (P value not reported) and overall substantial or total control of symptoms (P<0.001) compared to placebo. Budesonide produced a significant reduction in sneezing compared to fluticasone propionate (P=0.04). There were no other significant differences in individual nasal symptoms, combined nasal symptoms, eye symptoms, or overall substantial or total control of symptoms between treatment groups (P values not reported). Secondary: Budesonide and fluticasone propionate were well tolerated, with reported adverse events mild to moderate in severity.
Naclerio et al.[54] (2003) Budesonide 32 µg in each nostril QD	PG, RCT Patients >18 years of age with PAR, who were symptomatic on	N=20 2 weeks	Primary: Symptomatic relief and QoL as assessed by the RQLQ and nasal clearance	Primary: The RQLQ scores demonstrated that both budesonide and mometasone resulted in a significant improvement in QoL compared to baseline (P value not reported). There were no significant differences between treatment groups for any of the individual domains in the RQLQ (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 100 µg in each nostril QD	the majority of days of each year and had a positive skin test to dust mites		Secondary: Not reported	Data on nasal clearance could not be interpreted by the authors. Secondary: Not reported
Varshney et al.[55] (2012) Ciclesonide 200 µg once vs fluticasone propionate 200 µg once	DB, RCT, XO Patients ≥12 years of age with allergic rhinitis for ≥1 year	N=74 1 day	Primary: Sensory attributes, TNSS, patient preference and adverse events Secondary: Not reported	Primary: Significantly more patients preferred fluticasone propionate compared to ciclesonide with regard to satisfying scent (50.00 vs 8.11%; P<0.001) and "providing a more soothing feel" (56.76 vs 20.27%; P<0.001). Moreover, significantly fewer patients treated with fluticasone propionate compared to ciclesonide reported nasal irritation (1.35 vs 28.38%; P=0.002). The number of patients reporting immediate taste, aftertaste, run down to throat and run off from nose were less with ciclesonide compared to fluticasone propionate; however, the difference was not statistically significant. Treatment with either ciclesonide or fluticasone propionate decreased TNSS compared to baseline, as well as individual symptom scores in majority of the subjects, within 10 minutes of administration. The median (interquartile range) TNSS declined from eight (seven to nine) at baseline to three (two to four) following administration in patients treated with ciclesonide first. In the fluticasone first group, the corresponding decline was from eight (six to 10) to two (two to four). This difference was not statistically significant. Differences were also not significant when the proportions reporting decrease in individual symptom scores, rather than total score, were compared. Significantly more patients preferred treatment with fluticasone propionate compared to treatment with ciclesonide (55.41 vs 25.68%; P=0.007). Not all patients reported a preference for treatment. Overall, 9.46% of patients reported adverse events. Two patients reported minor headache following ciclesonide first, while three felt minor headache, one dizziness, and one nasal congestion following initial treatment with fluticasone propionate. No delayed adverse events were reported at the 24 hour follow-up interview.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Aasand et al.[56] (1982) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	MC, PG, SB Patients with ≥2-year history of SAR	N=47 4 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: Flunisolide and beclomethasone improved nasal rhinitis symptoms (88% of patients showed improvement with flunisolide vs 91% with beclomethasone; P value not reported). Secondary: The only reported adverse event with both medications was mild stinging of transient duration.
Langrick et al.[57] (1984) Flunisolide 200 µg daily, administered as 2 sprays in each nostril BID vs beclomethasone 400 µg daily, administered as 2 sprays in each nostril BID	PG, RCT, SB Patients 18 to 60 years of age, with a history of moderate to severe hay fever	N=69 7 weeks	Primary: Signs and symptoms of hay fever, severity of symptoms, and physicians' and patients' evaluation of overall effect of treatment Secondary: Adverse events	Primary: There were no significant differences between treatment groups in severity of symptoms, overall treatment effect, or patients' self-assessment of symptoms such as sneezing, runny nose and blocked nose (P value not reported). Secondary: One patient in the flunisolide group reported a dry throat of moderate severity. One patient in the beclomethasone group reported a mild tickling sensation inside the nose.
McAllen et al.[58] (1980) Flunisolide 50 µg in each nostril BID	SB, XO Patients 19 to 58 years with PAR with or without seasonal exacerbations and	N=34 8 weeks	Primary: Rhinitis symptoms Secondary: Adverse events and Candida growth	Primary: Treatment with flunisolide and beclomethasone significantly reduced sneezing, stuffiness, runny nose, nose-blowing and interference with routine life when compared to baseline (P value not reported). There were no statistical differences between the flunisolide and beclomethasone treatment groups in nasal symptoms, physicians' and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs beclomethasone 50 µg in each nostril QID	had moderate to severe symptoms			patients' preference, and interference with routine life (P value not reported). Secondary: Neither treatment resulted in Candida growth. Adverse events were minor and were mostly nasal irritation or dryness.
Sahay et al.[59] (1980) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	OL, PG Patients with PAR, with or without SAR	N=56 4 weeks	Primary: Symptom relief Secondary: Detection of Candida growths and safety	Primary: Flunisolide and beclomethasone resulted in significant reductions in sneezing, stuffiness, runny nose, nose blowing, postnasal drip, epistaxis and interference by symptoms with routine life or sleep compared to baseline (P<0.01 for all). There were no statistically significant differences in control of symptoms between the two treatment groups (P value not reported). Secondary: There were no signs of adrenal suppression or Candida growth in either group. There were four adverse events in the flunisolide group and five in the beclomethasone group that were considered to be probably drug related (P value not reported).
Sipila et al.[60] (1983) Flunisolide 50 µg in each nostril BID vs beclomethasone 50 µg in each nostril QID	OL, PG Patients with allergic rhinitis and seasonal symptoms for ≥2 years	N=45 4 weeks	Primary: Daily symptoms and severity of nasal symptoms Secondary: Adverse events	Primary: There were no significant differences between the treatment groups in the change from baseline in daily symptoms such as runny nose, stuffiness, sneezing, and eye symptoms (P value not reported). Improvement in the severity of nasal symptoms compared with baseline was similar in both treatment groups (P value not reported). Secondary: The reported adverse events were mild and primarily consisted of local irritation.
Kubavat et al.[61] (2011)	AC, MC, OL	N=220	Primary: Change from baseline	Primary: The mean change in TSS score was significantly greater for patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 110 µg QD vs fluticasone propionate 200 µg QD	Patients ≥18 years of age with complaints of allergic rhinitis with nasal/ocular symptoms	2 weeks	in TSS Secondary: Change from baseline in TNSS and TOSS, individual nasal and ocular symptoms	receiving fluticasone furoate compared to fluticasone propionate over two weeks (-10.4 vs -8.9; P<0.005). A significantly greater proportion of patients experienced complete relief from all nasal and ocular symptoms (i.e. a TSS of zero during the course of the study) with fluticasone furoate treatment compared to fluticasone propionate (45.3 vs 31.4%; P<0.05). Secondary; A statistically significant reduction in TNSS occurred with fluticasone furoate treatment compared to fluticasone propionate (-7.3 vs -6.2; P<0.05). There was no statistically significant difference in TOSS between fluticasone furoate treatment and fluticasone propionate following two weeks of treatment (-3.1 vs -2.7; P=NS). There were statistically significant improvements in symptom scores with fluticasone furoate compared to fluticasone propionate for nasal congestion (P<0.05), nasal itching (P<0.001) and tearing/watery eyes (P<0.05). There were no other statistically significant differences in individual symptom scores between the treatments (P=NS).
Meltzer et al.[62] (2010) Fluticasone furoate 100 µg QD for 1 week vs fluticasone propionate 200 µg QD for 1 week vs	DB, PC, RCT, XO Patients ≥18 years of age with SAR and nasal symptoms during previous fall allergy seasons and a positive skin test result and exposure to fall allergens	N=360 21 days	Primary: Patient preference at the end of the second XO period based on scent or odor Secondary: Patient preference at the end of the second XO period based on leaking out of the nose and down the throat, ease of use, and gentleness of mist, delivery of consistent	Primary: Twice as many patients preferred fluticasone furoate compared to fluticasone propionate based on scent or odor (P<0.001). Fifteen percent of patients had no preference for either product based on scent or odor. Secondary: Significantly more patients preferred fluticasone furoate compared to fluticasone propionate based on medication leaking out of the nose and down the throat, gentleness of the mist, and less aftertaste (P<0.001). No statistically significant differences were observed between products in ease of use, consistency of medication dose delivered, delivery method or device comfort.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			dose/use, comfort of nose tip, spray delivery method, aftertaste and TNSS	The TNSS were similar between treatment groups. Fluticasone furoate and fluticasone propionate significantly reduced TNSS compared to their respective placebo (P≤0.01). The proportion of patients with any adverse event was similar between treatments.
Meltzer et al.[63] (2008) Fluticasone furoate 110 µg as a single dose (FF) vs fluticasone propionate 200 µg as a single dose (FP) A ten minute washout period occurred between XO treatments.	DB, MC, RCT, XO Patients ≥18 years of age with allergic rhinitis	N=127 1 day	Primary: Overall patient preference Secondary: Patient preference for individual sensory attributes and their ratings	Primary: Significantly more patients favored fluticasone furoate compared to fluticasone propionate (P=0.003). Secondary: Significantly more patients favored fluticasone furoate compared to fluticasone propionate based on odor, taste, aftertaste drip down the throat and nose runoff (P≤0.037 for all). No significant differences were observed between groups with respect to whether the medication felt soothing, caused nasal irritation or caused sneezing.
Haye et al.[64] (1993) Fluticasone propionate 200 µg BID vs beclomethasone 200 µg BID	DB, MC, PG, RCT Patients ≥16 years of age with PAR	N=251 1 year	Primary: Rhinitis symptoms Secondary: Safety	Primary: Fluticasone propionate treatment resulted in significantly less nasal blockage (P=0.002), nasal discharge (P=0.002) and eye watering/irritation (P=0.048) compared to beclomethasone. No significant differences were observed in the amount of sneezing (P=0.114) or nasal itching (P=0.052) between treatment groups. Secondary: There were no significant differences in nasal itching (P=0.052), sneezing (P value not reported), nasal examination by rhinoscopy, hematologic, biochemical, and urinary parameters, plasma cortisol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				level or adverse events (P values not reported) between treatment groups.
LaForce et al.[65] (1994) Fluticasone propionate 100 µg BID or 200 µg QD vs beclomethasone 168 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with ≥2-year history of SAR, who have positive skin test to ≥1 spring allergen and moderate to severe symptoms	N=238 4 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: Fluticasone propionate reduced patient-rated nasal symptom scores significantly more than beclomethasone (P<0.05) and placebo (P<0.01) at all time points measured. There were no statistically significant differences in clinician-rated nasal symptom scores between treatment groups (P=NS). Secondary: There were no significant differences in adverse events between treatment groups (P value not reported).
Ratner et al.[66] (1992) Fluticasone propionate 200 µg QD vs beclomethasone 168 µg BID vs placebo	DB, MC, PC, PG, RCT Adult patients with ≥2-year history of SAR and moderate to severe symptoms and positive skin test to mountain cedar	N=313 2 weeks	Primary: Nasal symptoms, overall response to treatment, and use of rescue medication (chlorpheniramine) Secondary: Adverse events	Primary: Significant improvements in nasal symptoms and overall response to treatment were seen with fluticasone propionate and beclomethasone compared to placebo as evaluated by the clinicians and patients (P<0.05 for all). There were no statistically significant differences between treatment groups in nasal symptoms as rated by the clinicians or the patients or overall response to treatment (P value not reported). Compared to placebo, there was a significant reduction in the use of rescue medication with fluticasone propionate and beclomethasone (P<0.05). There was no statistically significant difference between treatment groups in the amount of rescue medication used (P value not reported). Secondary: No clinically significant differences in any of the safety variables between treatment groups were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Van As et al.[67] (1993) Fluticasone propionate 100 µg BID or 200 µg QD vs beclomethasone 168 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 to 71 years of age, with PAR and moderate to severe symptoms, nasal eosinophils, and positive skin test to a perennial allergen	N=466 6 months	Primary: Nasal symptoms and use of antihistamine as rescue medication Secondary: Adverse events	Primary: Fluticasone propionate and beclomethasone reduced nasal obstruction, rhinorrhea, sneezing, nasal itching and nasal eosinophilia compared to placebo (P value not reported). There were no significant differences between active treatment groups in nasal symptoms, number of patients who used rescue medication, amount of rescue medication consumed or incidences of adverse events (P value not reported). Secondary: No evidence of systemic effects with drug treatment was reported.
Okubo et al.[68] (2009) Fluticasone furoate 110 µg QD (FFNS) vs fluticasone propionate 100 µg BID (FPNS) vs placebo	DB, MC, PC, PG, RCT Patients ≥16 years of age with cedar pollinosis	N=446 2 weeks	Primary: Mean change in 3TNSS (the sum of three individual symptom scores for sneezing, rhinorrhea and nasal congestion), mean change in 4TNSS (the sum of scores for sneezing, rhinorrhea, nasal congestion and nasal itching), mean change in individual nasal symptom scores and rhinoscopy scores, patients' impression of treatment effect, and number of days until onset of action Secondary:	Primary: The mean change from baseline in 3TNSS over the entire treatment period was significantly greater for FFNS than for placebo (P<0.001). A significant decrease in 3TNSS was also observed in the FPNS group compared to placebo (P<0.001). Fluticasone furoate was non-inferior to fluticasone propionate in mean change from baseline in 3TNSS. There were similar mean changes in 4TNSS in the FFNS and FPNS groups. Mean changes from baseline in 4TNSS were significantly greater with FFNS and FPNS compared to placebo (both P<0.001). There were similar mean changes in individual nasal symptom scores (sneezing, rhinorrhea, nasal congestion, and nasal itching) in the FFNS and FPNS groups. There was a significant decrease in all symptom scores with FFNS compared with placebo (P<0.001). There were similar improvements in rhinoscopy findings, activity of daily life interference, and patient-rated overall evaluation to therapy in both groups. After two weeks of treatment, the number of patients who felt

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	"improved (improved, remarkably improved)" was highest with FFNS (50%), followed by FPNS (45%), FPNS placebo (14%), and then FFNS placebo (10%). There was a significant difference between the FFNS and FFNS placebo groups (P<0.001), suggesting improvement of ADL in the patients treated with FFNS. Secondary: Not reported
Bachert et al.[69] (2004) Fluticasone propionate 200 µg QD vs triamcinolone 220 µg QD vs placebo	DB, PC, RCT, XO Healthy volunteers 18 to 65 years of age	N=23 12 days	Primary: Suppression of the HPA axis as measured by 12-hour overnight urinary cortisol excretion and serum cortisol concentrations Secondary: Adverse events	Primary: Overnight urinary cortisol concentrations showed that there was no significant difference in HPA axis suppression with fluticasone propionate (P=0.609) or triamcinolone (P=0.194) compared to placebo. Neither fluticasone propionate (P=0.999) nor triamcinolone (P=0.521) showed a significant effect on the HPA axis activity when compared to placebo, as assessed by the mean peak serum cortisol concentrations before and after ACTH stimulation. Secondary: Both medications were well-tolerated. There were no significant differences in the number of subjects who experienced adverse events between treatment groups (one with fluticasone propionate, two with triamcinolone, three with placebo; P value not reported).
Ratner et al.[70] (2009) Mometasone 100 µg QD vs beclomethasone 168 µg QD	MC, SB, SC Children 6 to 11 years of age with ≥1 year history of PAR	N=255 12 months	Primary: Changes in overall PAR symptoms and response to treatment, as well as safety Secondary: Not reported	Primary: Physician-rated reductions in PAR symptoms were -42.1% for mometasone compared with -44.0% for beclomethasone. Subject-rated overall condition of PAR was -39.7% for mometasone compared with -39.0% for beclomethasone. A total of 94% of patients in the mometasone group reported mostly mild to moderate adverse reactions compared with 100% in the beclomethasone group. Epistaxis, headache, and pharyngitis were the most frequently reported events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no evidence of HPA axis suppression in children. Secondary: Not reported
Drouin et al.[71] (1996) Mometasone 100 µg in each nostril QD vs beclomethasone 100 µg in each nostril BID vs placebo	DB, DD, MC, PC, PG, RCT Patients ≥12 years of age who were allergic to ≥1 perennial allergen, with adequate symptomatology	N=427 12 weeks	Primary: Change from baseline in TNSS over the first 15 days of treatment Secondary: TNSS averaged over 15-day intervals beyond day 15, composite total and individual diary symptom scores, physician evaluation of response to therapy, and adverse events	Primary: When compared to placebo, both mometasone and beclomethasone produced significantly greater improvements in the TNSS over the first 15 days of treatment (P≤0.01). The difference in reduction from baseline in nasal symptom scores between mometasone and beclomethasone was not significant at any time point (P≥0.32). Secondary: Physician evaluations of nasal symptoms for mometasone and beclomethasone were not statistically different from each other at any time point (P value not reported). The rates of adverse events were similar for all groups (43% for mometasone, 42% for beclomethasone and 36% for placebo; P value not reported).
Graft et al.[72] (1996) Mometasone 100 µg in each nostril QD vs beclomethasone 84 µg in each nostril BID vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of moderate to severe SAR and a positive skin test response to ragweed	N=349 8 weeks	Primary: Severity score of nasal and non-nasal symptoms Secondary: Adverse events	Primary: Both treatments resulted in a significantly higher percentage of days with minimal symptoms, longer duration to the first occurrence of a non-minimal symptom day and TNSS compared with placebo (P≤0.01 for all). There was no statistically significant difference in the percentage of days with minimal symptoms between treatment groups (P value not reported). Nasal symptom scores for the treatment period prior to the allergy season onset were significantly lower with mometasone than beclomethasone (P=0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				The percentage of patients experiencing at least one adverse event that was considered possibly related to treatment was: 16% of the mometasone group, 14% of the beclomethasone group and 19% of the placebo group (P value not reported). The adverse events were generally mild to moderate and of short duration.
Hebert et al.[73] (1996) Mometasone 100 to 200 µg QD, administered as 2 sprays of 25 or 50 µg/spray in each nostril QD vs beclomethasone 100 µg in each nostril BID vs placebo	DB, DD, MC, PC, PG, RCT Patients ≥18 years of age with moderate to severe SAR who have a positive skin test to ≥1 tree and/or grass aeroallergen	N=501 4 weeks	Primary: Nasal symptom score, physicians' and patients' evaluation of response to therapy, and use of loratadine as rescue medication Secondary: Adverse events	Primary: Nasal symptoms (P≤0.01) and use of rescue medication (P≤0.05) were significantly improved in all three treatment groups compared to placebo. There were no significant differences between treatment groups in nasal symptom score, physicians' evaluation of nasal symptoms, overall condition, and response to treatment, or use of rescue medication (P value not reported). Secondary: The rate of adverse events were similar in all groups (25% with mometasone 100 µg, 26% with mometasone 200 µg, 30% with beclomethasone, 28% with placebo; P value not reported).
Mandl et al.[74] (1997) Mometasone 100 µg in each nostril QD vs fluticasone propionate 100 µg in each nostril QD	DB, DD, PC, PG, RCT Patients 12 to 77 years of age, who are allergic to ≥1 perennial allergen, and have moderate to severe symptomatology	N=550 12 weeks	Primary: Nasal symptom score Secondary: Physicians' evaluation of nasal symptoms and response to therapy and adverse events	Primary: Both mometasone and fluticasone propionate produced significantly greater improvements in nasal symptoms compared to placebo (P<0.01). The difference in reduction of nasal symptom score between mometasone and fluticasone propionate was not significant at any time point (-37 vs -39%, respectively; P≥0.43). Secondary: Physicians' evaluation of nasal symptoms and response to therapy were similar for mometasone and fluticasone propionate (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				The rates of adverse events were similar for all groups (33% for mometasone, 38% for fluticasone propionate and 37% for placebo; P value not reported).
Meltzer et al.[75] (2005) Mometasone vs fluticasone propionate 200 µg	DB, RCT, XO Patients with allergic rhinitis	N=100 Duration not specified	Primary: Individual product sensory attributes and overall sensory preference Secondary: Not reported	Primary: Significantly more patients preferred mometasone to fluticasone propionate for its scent (P=0.0005), immediate taste (P=0.005), aftertaste (P=0.005) and overall (54 vs 33%; P=0.03). Patients rated mometasone as significantly better than fluticasone propionate in individual sensory attributes, which included fewer perceived scent/odor (P<0.001), taste (P=0.002) and aftertaste (P=0.007). Patients reported significantly larger percentage of expected compliance with mometasone than fluticasone propionate (47 vs 25%; P=0.03). Secondary: Not reported
Mak et al.[76] (2013) Mometasone 100 µg QD vs fluticasone propionate 100 µg QD	AC, PRO, RCT Children 6 to 12 years of age with PAR for ≥2 years, a positive reaction to mite-specific IgE and allergy to dust mites confirmed by skin response to test	N=94 4 weeks	Primary: Change in TSS, PRQLQ, nPEFR and eosinophil percentage Secondary: Not reported	Primary: Patients treated with mometasone experienced statistically significant improvements in TSS for rhinorrhea (P=0.035), nasal stuffiness (P=0.029), nasal itching (P=0.031) and sneezing (P=0.009) compared to baseline. No significant improvements in nonnasal symptoms were reported (throat itching, eye itching, tearing and eye congestion; P>0.05 for all). Fluticasone propionate treatment significantly improved symptoms of nasal itching compared to baseline (P=0.007); however, no significant improvements in rhinorrhea, nasal stuffiness or nasal itching were reported (P>0.05 for all). Significant improvements in eye itching were also reported (P=0.014). Patients in both treatment groups experienced significant reductions from baseline in PRQLQ scores (P<0.01); however, the difference between the treatment groups was not statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.224). The mometasone group exhibited a significant improvement on the PRQLQ for all symptoms with the exception of swollen eyes (P=0.148) and sore eyes (P=0.086), thirst (P=0.056) and tiredness (P=0.09). The fluticasone propionate group also showed improvement in all categories excluding watery eyes (P=0.054) and sore eyes (P=0.291). Only the mometasone treatment group experienced a significant improvement in nPEFR at four weeks compared to baseline (P<0.05). There were statistically significant improvements from baseline in eosinophil percentage in nasal smears for both the mometasone (from 54.68±16.10 at baseline to 39.30±15.09; P<0.01) and fluticasone propionate (from 59.08±16.38 at baseline to 40.92±14.84; P<0.01). No significant differences were observed between the two groups (P=0.26). Secondary: Not reported
Lumry et al.[77] (2003) Triamcinolone 220 µg QD vs beclomethasone 168 µg BID	MC, PG, RCT, SB Patients ≥18 years of age with SAR to ragweed pollen for ≥2 years	N=152 3 weeks	Primary: Nasal symptoms, eye symptoms, HRQL, and patient preference for sensory attributes Secondary: Adverse events	Primary: Significant improvements from baseline in rhinitis related-nasal and eye symptoms were seen with triamcinolone and beclomethasone (P value not reported). There were no significant differences in nasal stuffiness, nasal discharge, nasal index, nasal itching, total eye symptoms, patients' or physicians' overall assessment of efficacy or HRQL between the treatment groups (P value not reported). Patients rated the taste and odor of triamcinolone as significantly better than beclomethasone (P≤0.05). Otherwise, there were no statistically significant differences between treatment groups in the other sensory attributes such as medication running down throat, medication running out of nose, medication induced sneezing, stinging/burning sensation, nose bleed, and blood in mucus (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: The rates of reported adverse events were comparable between treatment groups (34.7% with triamcinolone vs 35.1% with beclomethasone; P value not reported).
Winder et al.[78] (1993) Triamcinolone 220 µg QD vs beclomethasone 84 µg BID	MC, PG, RCT, SB Patients 18 to 64 years of age with PAR for ≥2 years who have positive skin tests to indoor allergens and nasal eosinophilia or basophilia	N=169 4 weeks	Primary: Rhinitis symptoms and global evaluations of treatment by patients and physicians Secondary: Adverse events	Primary: No statistically significant differences were reported in rhinorrhea, congestion, sneezing, sum of primary symptom scores or physicians' global evaluations between treatment groups (P value not reported). Patients' global evaluation of treatment with triamcinolone was significantly higher than with beclomethasone (P<0.05). Secondary: There were no statistically significant differences between treatments in burning/stinging, nasal dryness, nasal bleeding, bloody mucus, nasal congestion, throat discomfort and bad taste (P=NS). There was significantly more medication-induced sneezing with triamcinolone compared to beclomethasone (P=0.024). There was significantly more medication runoff from the nose and throat with beclomethasone than triamcinolone (P<0.05).
Gross et al.[79] (2002) Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril QD	AC, PG, RCT, SB Patients 12 to 70 years of age, with fall SAR and positive skin test to ragweed	N=352 3 weeks	Primary: Nasal symptoms, effects on HRQL as measured by RQLQ and adverse events Secondary: Not reported	Primary: No statistically significant differences were reported between the treatment groups in daily TNSS (P=0.332), individual symptom scores (P value not reported), treatment-related adverse events (P value not reported), overall HRQL scores (P=0.4) or overall RQLQ scores (P value not reported). Secondary: Not reported
Small et al.[80] (1997)	MC, PG, RCT, SB	N=233	Primary: Rhinitis Index Score	Primary: There were no significant differences between treatment groups in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril QD	Patients 12 to 70 years of age with spring pollen SAR for ≥2 years	21 days	and individual symptom score Secondary: Physicians' and patients' global evaluations, patients' acceptance of the study medications, and safety	change from baseline in Rhinitis Index Score (P=0.23) or individual symptoms, such as congestion (P=0.58), rhinorrhea (P=0.08), sneezing (P=0.51) and nasal itching (P=0.64). Secondary: There were no statistically significant differences between treatment groups in physicians' and patients' global evaluations (P value not reported). Fluticasone propionate was rated as significantly more intolerable than triamcinolone with respect to medication "running down the throat" and "medication running out of nose" (P<0.01). Triamcinolone was rated as significantly more intolerable than fluticasone propionate with respect to "medication causing dry nostril" and "medication causing stuffed-up nose" (P<0.01). Adverse events were experienced by 26% of the patients receiving triamcinolone and 22% of the patients receiving fluticasone propionate (P value not reported).
Berger et al.[81] (2003) Triamcinolone 110 µg in each nostril QD vs fluticasone propionate 100 µg in each nostril QD	AC, MC, PG, SB Patients 12 to 70 years of age with SAR for ≥2 years and a positive epicutaneous or intradermal test to 1 or more tests of grass pollen, tree pollen, and/or outdoor molds present in their environment	N=295 21 days	Primary: Mean TNSS Secondary: Mean individual symptom scores, dropout rate due to insufficient therapeutic effect, RQLQ scores and SAQ scores	Primary: Both triamcinolone and fluticasone propionate were effective at significantly reducing TNSS scores from baseline (P<0.05). After 21 days, there was no difference between treatments in regard to change in TNSS scores (95% CI, 0.7391 to 0.3693). Secondary: Both treatments were equally effective at reducing symptom scores from baseline including nasal discharge (P=0.9539), nasal stuffiness (P=0.7666), sneezing (P=0.5559) and nasal itching (P=0.7858). Zero patients discontinued study the study medications due to lack of therapeutic effect. There were no significant differences in mean overall RQLQ scores (P=0.54) or in individual domain scores between treatments. All changes were statistically significant compared to baseline scores (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On the SAQ, patients reported significantly less odor with triamcinolone compared to fluticasone propionate (12.3 vs 40.7%; P<0.0001).
Welsh et al.[82] (1987) Beclomethasone 336 µg/day, administered as 2 sprays in each nostril BID vs flunisolide 200 µg/day, administered as 2 sprays in each nostril BID vs cromolyn 41.6 mg/day, administered as 1 spray in each nostril QID vs placebo	PC, RCT Patients 12 to 50 years of age with ≥2 year history of SAR and positive skin test to crude short ragweed extract	N=120 8 weeks	Primary: Symptomatic relief Secondary: Adverse events	Primary: Beclomethasone, flunisolide and cromolyn significantly reduced the use of supplemental antihistamines or decongestants and hay fever symptoms such as sneezing, nasal symptoms, eye symptoms, itchy nose, and throat symptoms compared to placebo (P<0.001). Beclomethasone and flunisolide significantly reduced hay fever symptoms compared to cromolyn (P<0.001). There were no statistically significant differences between beclomethasone and flunisolide in relief of hay fever symptoms (P value not reported). Secondary: There was significantly more nasal burning with flunisolide compared to other treatments (P<0.001).
Stokes et al.[83] (2004) Triamcinolone 220 µg one time	DB, MC, RCT, XO Patients 18 to 70 years of age with	N=215 1 day	Primary: Patients' sensory perception measured by the NSEQ, patients' preference measured by	Primary: The NSEQ scores for triamcinolone were significantly higher than fluticasone propionate and mometasone (78.6 vs 72.3 and 69.3, respectively; P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 200 µg one time vs mometasone 200 µg one time	≥2-year history of allergic rhinitis, who were symptomatic at baseline		the ONSEQ, patients' self-reported expected compliance score using the four-point Likert scale Secondary: Not reported	Based on the ONSEQ scores, significantly more patients preferred triamcinolone (50% for triamcinolone, 25% for fluticasone propionate and 25% mometasone; P<0.001 for all). A larger percentage of the patients reported a Likert score of one or "definitely complying" with triamcinolone (62.5% for triamcinolone, 49.0% for fluticasone and 51.0% for mometasone; P<0.01 for all). Secondary: Not reported
Bachert et al.[84] (2002) Triamcinolone 110 µg in each nostril QD vs fluticasone 100 µg in each nostril QD vs mometasone 100 µg in each nostril QD	DB, MC, RCT, XO Patients ≥18 years of age with s ≥2-year history of allergic rhinitis	N=95 1 day	Primary: Sensory perceptions, patient preferences, and likelihood of compliance Secondary: Not reported	Primary: Overall, more patients preferred triamcinolone to fluticasone propionate (P≤0.05) and mometasone (P≤0.001). Patients preferred the odor, sensation of greater moisture, less aftertaste, and less irritation of triamcinolone to that of fluticasone propionate and mometasone (P<0.05 for all). Triamcinolone was preferred more than mometasone for the taste, comfort and less irritation (P<0.05 for all). Fluticasone propionate was also preferred more than mometasone in terms of taste, comfort and amount of irritation (P≤0.05). There were no significant differences between fluticasone propionate and mometasone in aftertaste and amount of irritation (P value not reported). Patients reported a higher likelihood of compliance with triamcinolone (67.4%) compared to fluticasone propionate and mometasone (54.7 and 49.5%, respectively; P value not reported). Secondary: Not reported
Khanna et al.[85] (2005)	SB, XO Patients with	N=114 Duration not	Primary: Sensory perceptions and patient reference	Primary: Significantly more patients preferred mometasone and reported less irritation, odor and aftertaste (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Beclomethasone vs budesonide vs fluticasone vs mometasone	allergic rhinitis	specified	Secondary: Not reported	Fluticasone propionate was reported by patients as having a significantly higher odor strength and amount of irritation (P values not reported). Eighty percent of the patients predicted better compliance with their preferred drug. Secondary: Not reported
Garris et al.[86] (2009) Fluticasone furoate, dose not specified vs budesonide, dose not specified vs mometasone, dose not specified vs triamcinolone, dose not specified	RETRO Patients ≥4 years of age with ≥1 one pharmacy claim for a branded intranasal corticosteroid between April 2007 and July 2007	N=793,349 10 months	Primary: Time to concomitant use of a prescription non-sedating antihistamine, montelukast, or ocular medications Secondary: Not reported	Primary: A higher proportion of patients in the fluticasone furoate cohort did not have concomitant prescription medication use during follow-up compared to the other cohorts. Patients in the fluticasone furoate cohort had, on average, a 21% lower risk of having a concomitant prescription for allergic rhinitis compared to the other cohorts (P<0.05). The risk reduction was the greatest for concomitant use of a non-sedating antihistamine followed by ocular medications (25 and 16% respectively; P<0.05). No significant difference was observed between the fluticasone furoate cohort, the combination cohort of any other branded corticosteroid, mometasone or triamcinolone in the time to use of montelukast. Secondary: Not reported
Ratner et al.[87] (2008)	DB, DD, MC, PG, R	N=151 2 weeks	Primary: Change from baseline in TNSS	Primary: Compared to baseline all three treatment groups significantly improved TNSS (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and placebo nasal spray once in the morning vs fluticasone nasal spray, 2 sprays in each nostril QD in the morning and placebo nasal spray BID vs azelastine nasal spray, 2 sprays in each nostril BID (Astelin®) and fluticasone nasal spray, 2 sprays in each nostril QD in the morning	Patients 12 years and older with a minimum 2-year history of allergy to Texas mountain cedar confirmed in the past year by positive skin test		Secondary: Change from baseline for each individual treatment day, change from baseline for each individual symptom score, change from baseline in the RQLQ, safety	In the azelastine, fluticasone and combination groups the mean improvement from baseline TNSS was 4.8±4.3, 5.2±4.6, and 7.4±5.6, respectively. The improvement from baseline TNSS was 27.1% with fluticasone, 24.8% with azelastine, and 37.9% with the combination (P<0.05 for the combination vs either agent alone). Compared to the azelastine and fluticasone there were absolute improvements of 11.0 (P=0.007) and 13.0% (P=0.02) with the combination, respectively. Secondary: Compared to either single treatment the combination was significantly more efficacious in treating the symptoms of congestion and itchy nose (P<0.05). Compared to fluticasone the combination was significantly more efficacious in treating the symptom of runny nose (P<0.05). Compared to azelastine the combination was significantly more efficacious in treating the symptom of sneezing (P<0.05). On study days three to 14 the combination was significantly more efficacious than azelastine alone (P<0.05). On study days four and six to 11 the combination was significantly more efficacious than fluticasone alone (P<0.05). Compared to baseline all three treatments significantly improved overall RQLQ as well as the individual domains of RQLQ (P<0.01). In the overall RQLQ score the mean change from baseline was greater for the combination (1.92) compared to azelastine (1.21) and fluticasone (1.40). The difference was significant compared with azelastine but not fluticasone. Bitter taste was the most common adverse event with azelastine (8.2 vs 2.0% in the fluticasone group and 13.5% in the combination group). In 4.1% of the azelastine group, 4.0% of the fluticasone group and 5.8% of the combination group headache was reported.
Meltzer et al.[88] (2012)	AC, MC, PC, PG, RCT	N=770	Primary: 12-hour rTNSS	Primary: Patients receiving the combination of azelastine and fluticasone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	Patients 12 years of age and older with moderate-to-severe SAR and a positive skin prick test to a local, prevalent, seasonal allergen and a 12-hour rTNSS of ≥8 at a minimum of three assessments during the lead-in period,	14 days	Secondary: Change in individual symptom scores, onset of action, 12-hour rTOSS and the RQLQ overall score	propionate experienced significant reductions in the mean rTNSS (-5.54) compared to fluticasone propionate (-4.55; P=0.038), azelastine (-4.54; P=0.032) and placebo (-3.03; P<0.001). Combination therapy improved the rTNSS score by 39% compared to fluticasone propionate alone. Secondary: Patients receiving combination therapy achieved significant improvement in all individual symptoms (nasal congestion, runny nose, itchy nose and sneezing) compared to placebo (P<0.001 for all), In particular, combination therapy significantly improved nasal congestion compared to azelastine and fluticasone propionate (P≤0.046). The azelastine-fluticasone propionate combination demonstrated a rapid onset of action, with a statistically significant improvement in the TNSS compared with placebo at 30 minutes following the first dose. The significant improvements in the TNSS over placebo were sustained at each subsequent evaluation point during the four-hour observation period. The mean improvement from baseline in the 12-hour rTOSS was significantly greater with combination therapy (-3.56) compared to fluticasone propionate (-2.68; P=0.009); however, there was no statistically significant difference compared to azelastine (-2.96; P=0.069). There was a significant increase in RQLQ score with combination therapy compared to both azelastine and placebo (P<0.05 for both), but not compared to fluticasone propionate.
Hampel et al.[89] (2010) Azelastine-fluticasone propionate 137/50 µg 1 spray in each	DB, MC, PC, PG, RCT Patients ≥12 years of age with a ≥2-year history of allergy to Texas	N=610 14 days	Primary: Change from baseline in 12-hour rTNSS Secondary: Change from baseline in individual symptom	Primary: The mean improvement from baseline TNSS was -5.31 with combination therapy compared to -3.25 with azelastine (P<0.01), -3.84 with fluticasone propionate (P<0.01) and -2.2 with placebo. Both azelastine and fluticasone monotherapy were also significantly more effective compared to placebo (P≤0.02 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nostril BID vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	mountain cedar pollen, as confirmed by a positive prick-puncture skin test result and a 12-hour reflective TNSS of ≥8/12 and a congestion score of 2 or 3		scores, TNSS on each study day, TOSS, individual ocular symptom scores, RQLQ and safety	Secondary: Combination therapy significantly improved the individual TNSS symptoms of nasal congestion, itchy nose, and sneezing compared to azelastine, fluticasone, or placebo (P<0.05 for all). Combination therapy significantly improved runny nose compared to azelastine and placebo (P<0.01), but not compared to fluticasone. The combination of azelastine and fluticasone was associated with statistically significant improvements in TNSS on all study days compared to azelastine and placebo (P≤0.01 for both). Combination therapy improved TNSS compared to fluticasone propionate on all days except days 10 and 11 (P≤0.01). Patients treated with combination therapy significantly improved overall TOSS scores compared to patients randomized to either fluticasone or placebo (P<0.01); however, the difference between combination therapy and azelastine was not statistically significant. Combination therapy significantly improved individual ocular symptoms compared to azelastine, fluticasone, or placebo, with the exception of azelastine for watery eyes (P<0.05). The combination of azelastine and fluticasone significantly improved the overall RQLQ score compared to azelastine (P<0.05) and placebo (P<0.001) but not fluticasone (P=0.29). The most commonly reported adverse events were bitter taste (2.0% with azelastine, 0.0% with fluticasone, and 7.2% with combination therapy). No significant changes in vital signs were reported.
Carr et al.[90] (2012) Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID	MA (3 RCT) Subjects ≥12 years of age with a ≥2 year history of moderate-to-severe SAR and current clinical	N=3,398 14 days	Primary: Change from baseline in the AM and PM sum rTNSS score Secondary: Change from baseline in iTNSS, rTOSS and	Primary: Over the entire 14-day treatment period, combination treatment with azelastine-fluticasone propionate significantly reduced the mean rTNSS sum from baseline compared to azelastine, fluticasone and placebo (-5.7 vs -4.1, -5.1 and -3.0, respectively; P<0.001 for all). Secondary: Patients randomized to receive combination therapy achieved

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs azelastine 137 µg 1 spray in each nostril BID vs fluticasone propionate 50 µg 1 spray in each nostril BID vs placebo	rhinitis symptoms, a positive skin prick test response to relevant pollen and a rTNSS of at least 8/12, with a congestion score of 2 or 3 during screening		RQLQ	significant reductions in iTNSS scores (-5.2) compared to azelastine (-4.1; P<0.001), fluticasone (-4.8; P=0.022) and placebo (-2.6; P<0.001). More patients receiving combination therapy (12.4%) also exhibited complete or near-complete elimination of their symptoms (e.g., reduction in all nasal symptoms scores to <1) compared to those treated with fluticasone (9.3%; P=0.033), azelastine (7.1%; P<0.001), or placebo (4.2%; P<0.001). Over the entire 14-day treatment period, combination treatment reduced the mean rTOSS score from baseline was significantly greater with combination therapy (-3.2) compared to fluticasone (-2.8; P=0.003) and placebo (-1.8; P<0.001), but not compared to monotherapy with azelastine (-2.9; P=0.196). By day 14 of treatment, all three active treatment groups significantly improved RQLQ scores compared to placebo (P<0.001 for all).
Berger et al.[91] (2016) Azelastine-fluticasone propionate 137/50 µg 1 spray in each nostril BID vs placebo	DB, MC, PC, RCT Children 4 to 11 years of age with moderate or severe SAR	N=348 14 days	Primary: Change from baseline in morning and evening rTNSS in patients six to 11 years of age Secondary: Change from baseline in rTOSS, rT7SS (i.e. rTNSS + rTOSS; max score; 42), and individual nasal and ocular symptoms (each scored 0 to 3; AM and PM)	Primary: There was no statistically significant difference between treatment and placebo groups for overall change from baseline in rTNSS (AM + PM). Children in the treatment group experienced a −3.70 point reduction from baseline compared to −2.90 in the placebo group (difference, −0.80; 95% CI, −1.75 to 0.15; P=0.099). Secondary: As the extent of children's self-rating increased, so too did the treatment difference between azelastine-fluticasone and placebo; Azelastine-fluticasone provided significantly better relief than placebo for rTNSS (P=0.002), rTOSS (P=0.009) and each individual nasal and ocular symptom assessed (except rhinorrhea; P=0.064) when children mostly rated their own symptoms.
Treatment of chronic sinusitis				
Sindwani et al.[92] (2019) NAVIGATE I	DB, MC, PC, RCT Adults with	N=323 16 weeks	Primary: Coprimary end points were mean change in average morning	Primary: All three doses of fluticasone significantly improved both coprimary end points versus placebo (P<0.05, all comparisons). For instantaneous am congestion at week four, the least squares mean change from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone exhalation delivery system 93 µg, 186 µg, or 372 µg twice daily vs placebo exhalation delivery system	chronic rhinosinusitis with nasal polyps with moderate-severe symptoms and bilateral nasal polyposis		congestion score ("instantaneous am congestion," rated from 0 = no symptoms to 3 = severe) over 7 days prior to week 4; and mean change in endoscopically assessed total polyp grade (sum of scores, rated 0–3 on each side, from both nasal cavities) at week 16 Secondary: Change from baseline to week 16 in symptoms and functioning, measured by total Sino-Nasal Outcome Test-22 (SNOT-22) score	baseline was −0.49, −0.54, and −0.62, in the fluticasone 93 µg, 186 µg, and 372 µg groups, respectively, compared to −0.24 with placebo (P<0.01, all comparisons). For change in summed nasal polyp grade at week 16, the least squares mean change from baseline was −0.96, −1.03, and −1.06 in the fluticasone 93 µg 186 µg, and 372 µg groups, respectively, compared to −0.45 with placebo (P<0.01, all comparisons). Increasing doses of fluticasone produced numerically greater improvements in congestion and polyp grade, with the 372-µg dose resulting in the largest mean reduction in both, although between-dose differences did not reach statistical significance. Secondary: SNOT-22 improvement was substantial in all fluticasone groups and statistically superior to placebo (−18.3 to −19.8 for fluticasone vs −11.0 for placebo at week 16, P≤0.005, all comparisons).
Kern et al.[93] (2018) RESOLVE II Mometasone 1350 µg sinus implant (Sinuva) vs sham treatment Both groups also took mometasone nasal spray 200	DB, MC, PG, RCT Adults with a confirmed diagnosis of chronic rhinosinusitis with nasal polyps based on symptoms and endoscopic examination, had undergone prior endoscopic sinus	N=300 90 days	Primary: Co-primary efficacy endpoints were the change from baseline to day 30 in nasal obstruction/congestion score, as determined by patients, and change from baseline to day 90 in bilateral polyp grade, as determined by the independent, blinded panel Secondary:	Primary: Patients receiving implants demonstrated significant reductions in both nasal obstruction/congestion score (P=0.0074) and bilateral polyp grade (P=0.0073) compared to control. Secondary: At day 90, implants were associated with significant reductions in four of the five prespecified secondary endpoints compared to control. Fewer patients receiving implants than sham remained indicated for repeat endoscopic sinus surgery based on the prespecified study criteria (39.0% vs 63.3%, P=0.0004). Patients treated with implants also had a greater decrease in percent ethmoid sinus obstruction (P=0.0007) and experienced sustained symptomatic improvements in nasal obstruction/congestion (P=0.0248) and sense of smell (P=0.0470), but not in facial pain/pressure (P=0.9130).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg once daily	surgery, including bilateral total ethmoidectomy, and were currently indicated for repeat endoscopic sinus surgery		(1) nasal obstruction/congestion score change from baseline to day 90; (2) change in percent ethmoid sinus obstruction at day 90, as determined by the independent, blinded panel; (3) decreased sense of smell score change from baseline to day 90, as determined by patients; (4) facial pain/pressure score change from baseline to day 90, as determined by patients; and (5) proportion of patients still indicated for repeat endoscopic sinus surgery at day 90	
Treatment of Nonallergic Rhinitis				
Scadding et al.[94] (1995) Fluticasone propionate 200 µg QD or BID vs beclomethasone 200 µg BID vs	DB, MC, PC, PG, RCT Patients with allergic and nonallergic perennial rhinitis	N=not specified 12 weeks	Primary: Nasal symptoms Secondary: Adverse events	Primary: There were no significant differences between active treatment groups in regard to nasal symptoms (P value not reported). Secondary: Few adverse events and no treatment-related abnormalities in laboratory measurements were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MC=multi-center, NI=non inferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blinded, XO=cross-over
Miscellaneous abbreviations: ACTH=adrenocorticotropic hormone, ECG=electrocardiogram, ECP=eosinophil cationic protein, HRQL=health related quality of life, HPA=hypothalamic-pituitary-adrenal, IgE=immunoglobulin E, iTNSS=instantaneous total nasal symptom score, iTOSS=instantaneous total ocular symptom score, LS=least square, NSEQ=nasal spray evaluation questionnaire, nPEFR=nasal peak expiratory flow rate, ONSEQ=overall nasal spray evaluation questionnaire, PANS=physician assessed overall nasal signs and symptoms, PAR=perennial allergic rhinitis, PNIF=peak nasal inspiratory flow, PNSS=physician-assessed nasal symptom score, PRQLQ=pediatric rhinoconjunctivitis quality of life questionnaire, QoL=quality of life, rNNSS= reflective non-nasal symptom score, RQLQ=rhinoconjunctivitis quality of life questionnaire, rTNSS=reflective total nasal symptom score, rTOSS=reflective total ocular nasal symptom score, SAQ=sensory attributes questionnaire, SAR=seasonal allergic rhinitis, T5SS=total five symptom score, TNNSS=total nonnasal symptom score, TNSS=total nasal symptom score, TOSS=total ocular symptom score, TSS=total symptom score

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Corren et al. demonstrated that asthmatic patients with concomitant allergic rhinitis who were treated with nasal corticosteroids had a significantly lower risk of asthma exacerbations that resulted in emergency room visits (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.62 to 0.91) and hospitalizations (OR, 0.56; 95% CI, 0.42 to 0.76).[95] Bonfils et al. conducted a retrospective review of medical records and determined that 85% of patients were successfully treated with a short-term combination therapy of prednisolone and intranasal beclomethasone; therefore, they did not have to undergo surgery for nasal polyps.[96]

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 11. Relative Cost of the Intranasal Corticosteroids

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Beclomethasone	aerosol nasal spray, nasal spray	Beconase AQ®, QNASL®	$$$$$	N/A
Ciclesonide	aerosol nasal spray, nasal spray	Omnaris®, Zetonna®	$$$$$	N/A
Flunisolide	nasal spray	N/A	N/A	$$$
Fluticasone propionate	nasal spray	Xhance®	$$$$$	$
Mometasone	nasal implant, nasal spray	Sinuva®	$$$$$	$$
Combination Products				
Azelastine and fluticasone	nasal spray	Dymista®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

Intranasal corticosteroids are used for the management of allergic rhinitis, some forms of nonallergic rhinitis, and nasal polyps. They are generally well tolerated and are associated with limited drug interactions due to their localized administration and limited systemic absorption. Like other corticosteroids, intranasal corticosteroids carry warnings regarding the use in patients with active infection and the development of signs of adrenal insufficiency with the administration of higher than recommended doses.[11-13]

Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe persistent symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another. [2,16-19] All the available intranasal corticosteroids have demonstrated safety and efficacy for their respective indications. These agents have been shown to be effective in reducing rhinitis-related nasal symptoms such as congestion, rhinorrhea, sneezing, nasal itch, and postnasal drip. The differences in tolerability and sensory perceptions noted in clinical trials were minor and did not translate into improved outcomes. The results of multiple head-to-head trials have generally failed to demonstrate clinically significant differences between products.[20-91]

Mometasone is Food and Drug Administration (FDA)-approved for use in children two years of age and older, and fluticasone propionate and beclomethasone (QNASL®) are FDA-approved for use in children four years of age and older. Beclomethasone (Beconase AQ®), ciclesonide (Omnaris®), and flunisolide are approved for use in children six years of age and older.[3-13] The combination product of azelastine and fluticasone propionate (Dymista®) is approved for use in children six years of age and older.[10] Two nasal aerosol formulations of existing drugs, beclomethasone (QNASL®) and ciclesonide (Zetonna®), have been approved by the FDA for the relief of symptoms associated with perennial and season allergic rhinitis. The other intranasal corticosteroid products are formulated as aqueous suspensions which may be bothersome to patients due to the potential of the suspension to drip down or out of the nose following administration[12] Two new dosage formulations have been approved for the treatment of nasal polyps in patients 18 years of age and older, Xhance® (fluticasone propionate nasal spray) and Sinuva® (mometasone furoate sinus implant).[7,9] Xhance® is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the device.[7] Sinuva® is to be inserted in the ethmoid sinus under endoscopic visualization by physicians trained in otolaryngology.[9]

Comparative clinical trials have demonstrated similar efficacy with the intranasal steroids for the majority of the endpoints assessed in patients with allergic rhinitis. The differences in potencies, systemic bioavailabilities, and onset of action did not translate to improved efficacy. However, there were subtle differences reported among the various agents in tolerability and patient preference. Guidelines do not give preference to one intranasal corticosteroid over another for the treatment of allergic rhinitis.[2,15-19]

There is insufficient evidence to support that one brand intranasal corticosteroid is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand intranasal corticosteroids within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand intranasal corticosteroid is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antiallergic Agents
AHFS Class 520200
August 10, 2022

I. Overview

The eye, ear, nose, and throat (EENT) antiallergic agents include nasal and ophthalmic formulations, which are approved for the treatment of allergic conjunctivitis and rhinitis.[1-12] Conjunctivitis is an inflammatory condition of the conjunctiva, which may be classified as infectious or non-infectious. The types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Seasonal allergic conjunctivitis is precipitated by environmental allergens and the symptoms are usually mild and recurrent.[13] Vernal conjunctivitis usually occurs in hot, dry environments. Potential sequelae include 1) eyelid thickening, 2) ptosis, 3) conjunctival scarring, 4) corneal neovascularization, thinning, ulceration, and infection, 5) vision loss, and 6) keratoconus.[13] It is a chronic condition with acute exacerbations during spring and summer. The onset of vernal conjunctivitis typically occurs during childhood, with a gradual decrease in activity observed within two to 30 years. Allergic rhinitis is an inflammatory condition involving the nasal passages in response to an allergen. The severity of symptoms ranges from mild and intermittent to seriously debilitating. Nasal symptoms include congestion, rhinorrhea (anterior and posterior), sneezing, and itching. Patients may also experience symptoms of allergic conjunctivitis. The symptoms may decrease quality of life by causing headache, cognitive impairment, and fatigue.[14]

Cetirizine is a histamine H_1-receptor antagonist. Cromolyn, lodoxamide, and nedocromil are mast cell stabilizers. Azelastine, bepotastine, epinastine, and olopatadine are antihistamines with mast cell stabilizing properties.[1,2]

The EENT antiallergic agents that are included in this review are listed in Table 1. This review encompasses all EENT dosage forms and strengths. Azelastine, cromolyn, epinastine, and olopatadine are available in a generic formulation. Cromolyn is also available over-the-counter. This class was last reviewed in May 2020.

Table 1. EENT Antiallergic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azelastine	solution*†‡	N/A	azelastine
Bepotastine	solution*	Bepreve®	Bepreve®
Cetirizine	solution*	Zerviate®	none
Cromolyn	solution*‡	N/A	cromolyn*
Epinastine	solution*‡	N/A	epinastine
Lodoxamide	solution*	Alomide®	none
Nedocromil	solution*	Alocril®	none
Olopatadine	solution*†‡	Patanase®†‡,	olopatadine

*Ophthalmic formulation.
†Nasal formulation.
‡Generic is available in at least one dosage form and/or strength.
N/A=not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) antiallergic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the EENT Antiallergic Agents

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)[15]**	Pharmacologic treatment of allergic rhinitis • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma & Immunology: **Allergic Rhinitis and its Impact on Asthma**	Should a combination of an oral H_1-antihistamine and intranasal corticosteroid vs intranasal corticosteroid alone be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an oral H_1-antihistamine or an intranasal corticosteroid alone is suggested (low certainty of evidence).

Clinical Guideline	Recommendation(s)
(ARIA) guidelines-2016 revision (2016)[16]	• In patients with perennial allergic rhinitis, an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H_1-antihistamine is suggested (very low certainty of evidence). • This recommendation concerns regular use of newer and less sedative oral H_1-antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis. For older oral H_1-antihistamines with more sedative effects, the balance of desirable and undesirable effects may be different. • Currently available evidence suggests that there is no additional benefit from a combination therapy compared with intranasal corticosteroid alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (very low certainty of evidence). • At initiation of treatment (approximately the first two weeks), a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine might act faster than an intranasal corticosteroid alone and thus might be preferred by some patients. The choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal H_1-antihistamine alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine rather than an intranasal H_1-antihistamine alone is suggested (low certainty of evidence). <u>Should a leukotriene receptor antagonist vs an oral H_1-antihistamine be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a leukotriene receptor antagonist or an oral H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an oral H_1-antihistamine rather than a leukotriene receptor antagonist is suggested (low certainty of evidence). • The choice of a leukotriene receptor antagonist or oral H_1-antihistamine will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an oral H_1-antihistamine might still be more cost-effective, but this will largely depend on availability of generic leukotriene receptor antagonists and the local cost of various newer-generation oral H_1-antihistamines and leukotriene receptor antagonists. • Some patients with allergic rhinitis who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from a leukotriene receptor antagonist more than from an oral H_1-antihistamine. However, this recommendation applies to treatment of allergic rhinitis but not to treatment of asthma. Patients with asthma who have concomitant allergic rhinitis should receive an appropriate treatment according to the guidelines for the treatment of asthma.

Clinical Guideline	Recommendation(s)
	Should an intranasal H_1-antihistamine vs an intranasal corticosteroid be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (low certainty of evidence). Should an intranasal H_1-antihistamine vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (very low certainty of evidence). • The choice of treatment will depend mostly on patient preferences, local availability, and cost of treatment.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[14]	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Oral antihistamines • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. Intranasal antihistamines • Intranasal antihistamines may be considered for use as first-line treatment for

Clinical Guideline	Recommendation(s)
	allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis.

Clinical Guideline	Recommendation(s)
	• Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. Oral corticosteroids • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. Intranasal cromolyn • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. Intranasal anticholinergics • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. Oral antileukotriene agents • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. Omalizumab • Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Treatment of seasonal allergic**	For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age: • Routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine. • An intranasal corticosteroid is recommended over a leukotriene receptor antagonist (for ≥15 years of age). • For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.

Clinical Guideline	Recommendation(s)
rhinitis, an evidence-based focused 2017 guideline update (2017)[17]	
American Academy of Allergy, Asthma & Immunology: **Rhinitis 2020: A practice parameter update (2020)[18]**	• Prescribing first-generation antihistamines is not recommended; a second-generation antihistamine is preferred when prescribing an oral antihistamine for the treatment of AR. • Clinician should not select the oral LTRA montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies. • Clinicians should not select an oral LTRA for the treatment of NAR. • For the treatment of very severe or intractable AR, the clinician may consider a short course (5 to 7 days) of oral corticosteroids. • For the treatment of very severe or intractable AR, the clinician should not prescribe a depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects. • The clinician should offer intranasal antihistamine as an initial treatment option for patients with SAR. • The clinician should offer intranasal antihistamine as a first-line monotherapy option for patients with NAR. • The clinician should offer intranasal antihistamine as a first-line option for patients with intermittent AR. • When choosing monotherapy for persistent AR, intranasal corticosteroid should be the preferred medication. • For the initial treatment of moderate/severe SAR in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over an LTRA. • The use of intranasal decongestants should be short term and be used for intermittent or episodic therapy of nasal congestion. • In patients having severe mucosal edema, which impairs the delivery of other intranasal agents, an intranasal decongestant should be considered for up to five days of use. • Oral decongestant agents should be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome. • Oral decongestants should be avoided during the first trimester of pregnancy. • Patients with PAR and NAR who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium. • Intranasal cromolyn should be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures. • Clinicians should consider the combination of an intranasal corticosteroid and an internasal antihistamine for the initial treatment of moderate/severe nasal symptoms of SAR in patients age ≥12 years. • Clinicians should consider the combination of an intranasal corticosteroid and an intranasal antihistamine for moderate/severe SAR, PAR and NAR that is resistant to pharmacologic monotherapy. • For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium. • Patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to four weeks. • For patients with AR and nasal congestion uncontrolled with an oral

Clinical Guideline	Recommendation(s)
	antihistamine, the clinician should consider the addition of pseudoephedrine, when tolerated. • For SAR, the clinician should not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine. • The clinician should not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients ≥12 years of age with symptoms of SAR. • Clinicians should not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR. • The addition of the oral LTRA montelukast to an intranasal corticosteroid for AR is not recommended. • Clinicians should offer an intranasal corticosteroid as a first-line therapy for NAR. • Clinicians should offer an intranasal antihistamine as a first-line therapy for NAR. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be offered through shared decision making to patients with moderate/severe AR who are not controlled with allergen avoidance and/or pharmacotherapy or choose immunotherapy as the preferred method of treatment and/or desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be considered for patients with controlled mild and moderate asthma with coexisting AR.
American Academy of Otolaryngology - Head and Neck Surgery Foundation: **Clinical Practice Guideline Allergic Rhinitis (2015)**[19]	• The clinical diagnosis of allergic rhinitis (AR) should be made when patients present with a history and physical exam consistent with an allergic cause and one or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. • Patients with a clinical diagnosis of AR who do not respond to empiric treatment, or in whom the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy, should have specific IgE (skin or blood) allergy testing. • Sinonasal imaging should not routinely be performed in patients presenting with symptoms consistent with a diagnosis or AR. • AR patients who have identified allergens that correlate with clinical symptoms may avoid known allergens or utilize environmental controls. • Patients with AR should be assessed for the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. • Intranasal steroids are recommended for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. • Oral second-generation/less-sedating antihistamines are recommended for patients with AR and primary complaints of sneezing and itching. • Intranasal antihistamines may be used in patients with seasonal, perennial, or episodic AR. • Oral leukotriene receptor antagonists should not be offered as primary therapy for patients with AR. • Combination pharmacologic therapy may be used in patients with AR who have inadequate response to pharmacologic monotherapy. • Immunotherapy (sublingual or subcutaneous) should be offered to patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.

Clinical Guideline	Recommendation(s)
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2018)**[13]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • The use of topical mast-cell inhibitors can also be helpful in alleviating the symptoms of allergic rhinitis. Mast-cell inhibitors formulated as a nasal spray and aerosols are also helpful in alleviating the symptoms of allergic rhinitis and asthma in some patients. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a topical corticosteroid with a low side effect profile can be added to the regimen. • Oral antihistamines are commonly used but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and actually worsen allergic conjunctivitis. • Concomitant use of cooled artificial tears may alleviate coexisting tear deficiency and dilute allergens and inflammatory mediators on the ocular surface. • In severe cases, topical cyclosporine or tacrolimus can be considered. Vernal/atopic conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. Systemic immunosuppression is rarely warranted, but options include montelukast, aspirin, interferons, and oral T-cell inhibitors, such as cyclosporine and tacrolimus. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
College of Optometrists: **Clinical Management Guideline on Bacterial Conjunctivitis (2021)**[20]	Etiology • Self-limiting bacterial infection of the conjunctiva, typically by: o *Staphylococcus* species o *Streptococcus pneumoniae* o *Haemophilus influenzae* o *Moraxella catarrhalis* Predisposing factors • Children and the elderly have an increased risk of infective conjunctivitis o contamination of the conjunctival surface o superficial trauma o contact lens wear (infection may be Gram-negative) o secondary to viral conjunctivitis o diabetes (or other disease compromising the immune system) o steroids (systemic or topical, compromising ocular resistance to infection) o blepharitis (or other chronic ocular inflammation)

Clinical Guideline	Recommendation(s)

	Symptoms
	• Acute onset of:
	  ○ redness
	  ○ discomfort, usually described as burning or grittiness
	  ○ discharge (may cause temporary blurring of vision)
	  ○ crusting of lids (often stuck together after sleep and may have to be bathed open)
	• Usually bilateral – one eye may be affected before the other (by one or two days)
	
	Management by optometrist
	• Practitioners should recognize their limitations and where necessary seek further advice or refer the patient elsewhere
	• Non pharmacological
	  ○ Often resolves in five to seven days without treatment
	  ○ Bathe/clean the eyelids with proprietary sterile wipes, lint or cotton wool dipped in sterile saline or boiled (cooled) water to remove crusting
	  ○ Advise patient that condition is contagious (do not share towels, etc.)
	• Pharmacological
	  ○ Treatment with topical antibiotic may improve short-term outcome and render patient less infectious to others
	  ○ Topical antibiotics (with no evidence of superiority of particular antibiotics) may include: chloramphenicol 0.5% eye drops, chloramphenicol 1% ointment, azithromycin 1.5% eye drops, fusidic acid 1% viscous eye drops (note high cost and narrower spectrum of activity than chloramphenicol)
	  ○ Predictors of bacterial culture positivity at presentation include purulent discharge and age less than five years
	  ○ Contact lens wearers with a diagnosis of bacterial conjunctivitis should be treated with a topical antibiotic effective against Gram-negative organisms, e.g. a quinolone such as levofloxacin or moxifloxacin, or an aminoglycoside such as gentamicin. Contact lenses should not be worn during the treatment period
	  ○ Advise patient to return/seek further help if symptoms persist beyond seven days
	
	Possible management by ophthalmologist
	• If resistant to treatment, or recurrent:
	  ○ conjunctival swabs taken for microscopy and culture and/or polymerase chain reaction analysis
	  ○ treatment with other antibiotics, based on culture results

III. Indications

The Food and Drug Administration (FDA)-approved indications for the eye, ear, nose, and throat (EENT) antiallergic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the EENT Antiallergic Agents[3-12]

Indication(s)	Azelastine	Bepotastine	Cetirizine	Cromolyn	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Conjunctivitis								
Prevention of itching due to allergic conjunctivitis					✔			
Treatment of itching associated with allergic conjunctivitis	✔ *	✔	✔				✔	✔ †
Treatment of signs and symptoms of allergic conjunctivitis								✔ ‡
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis				✔ *		✔		
Rhinitis								
Prevent and relieve nasal symptoms of hay fever and other nasal allergies				✔ §				
Relief of the symptoms of seasonal and perennial allergic rhinitis	✔ ‖							
Treatment of the symptoms of seasonal allergic rhinitis	✔ ¶							✔ §
Treatment of the symptoms of vasomotor rhinitis	✔ ¶							

*Ophthalmic formulation.
†0.2% and 0.7%ophthalmic solution.
‡0.1% ophthalmic solution.
§Nasal formulation.
‖Astepro® nasal formulation.
¶ Astelin® nasal formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Antiallergic Agents[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Azelastine	N: 40 O: not reported	N: not reported O: 78 to 97	Liver, extensive (% not reported)	Renal (25) Feces (50 to 75)	22 to 25†
Bepotastine	Not reported	55	Liver, minimal (% not reported)	Renal (75 to 90)	Not reported
Cetirizine	Not reported	Not reported	Not reported	Not reported	8.2 to 8.6
Cromolyn	N: <7 O: <1	Not reported	Not metabolized	Renal (30 to 50) Feces (80 to 87)	<1†
Epinastine	Minimal (% not reported)	64	Liver (% not reported)	Renal (55)*	12
Lodoxamide	Not detectible (% not reported)	Not reported	Not reported	Not reported	8.5
Nedocromil	<4	Not reported	Not metabolized	Renal (70)	1.5 to 3.3†
Olopatadine	N: 57 O: minimal (% not reported)	N: 55 O: not reported	Not reported	N: Renal (70) Feces (17) O: Renal (60 to 70)	N: 8 to 12 O: 3

N=nasal formulation, O=ophthalmic formulation
*Metabolite.
†Based on oral, inhalation or intravenous administration.

V. Drug Interactions

There are no significant drug interactions with the eye, ear, nose, and throat (EENT) antiallergic agent.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the EENT Antiallergic Agents[3-12]

Adverse Events	Azelastine	Bepotastine	Cetirizine	Cromolyn	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Cardiovascular								
Atrial fibrillation	<1*	-	-	-	-	-	-	-
Chest pain	<1*	-	-	-	-	-	-	-
Flushing	<2*	-	-	-	-	-	-	-
Hypertension	<2*	-	-	-	-	-	-	-
Palpitation	<1*	-	-	-	-	-	-	-
Tachycardia	<2*	-	-	-	-	-	-	-
Central Nervous System								
Abnormal thinking	<2*	-	-	-	-	-	-	-
Anxiety	<2*	-	-	-	-	-	-	-
Confusion	<1*	-	-	-	-	-	-	-
Depersonalization	<2*	-	-	-	-	-	-	-
Depression	<2*	-	-	-	-	-	-	-
Dizziness	2*	-	-	-	-	<1	-	-
Drowsiness	<2*	-	-	-	-	-	-	-
Dysesthesia	8*	-	-	-	-	-	-	-
Fatigue	2*; 1 to 10†	-	-	-	-	-	-	-
Fever	<2*	-	-	-	-	-	-	-
Headache	8 to 15‡; 1 to 3§;15†	2 to 5	-	1 to 10*	1 to 3	<2	40	<7†
Heat sensation	-	-	-	-	-	<1	-	-
Hypoesthesia	<2*	-	-	-	-	-	-	-
Malaise	<2*	-	-	-	-	-	-	-
Nervousness	<2*	-	-	-	-	-	-	-
Paresthesia	<1*	-	-	-	-	-	-	-
Sleep disorder	<2*	-	-	-	-	-	-	-
Somnolence	<1 to 12*	-	-	-	-	<1	-	1*
Vertigo	<2*	-	-	-	-	-	-	-
Dermatological								
Contact dermatitis	<2*	-	-	-	-	-	-	-
Eczema	<2*	-	-	-	-	-	-	-
Facial edema	<1*	-	-	-	-	-	-	-
Furunculosis	<2*	-	-	-	-	-	-	-
Hair and follicle infection	<2*	-	-	-	-	-	-	-
Pruritus	<1*	-	-	-	-	-	-	-
Skin irritation	<1*	-	-	-	-	-	-	-

Adverse Events	Azelastine	Bepotastine	Cetirizine	Cromolyn	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Skin laceration	<2*	-	-	-	-	-	-	-
Endocrine and Metabolic								
Amenorrhea	<2*	-	-	-	-	-	-	-
Breast pain	<2*	-	-	-	-	-	-	-
Gastrointestinal								
Abdominal pain	<2*	-	-	-	-	-	-	-
Aphthous stomatitis	<2*	-	-	-	-	-	-	-
Appetite increased	<2*	-	-	-	-	-	-	-
Bitter taste	8 to 20*; 6 to 7†	-	-	-	-	-	-	13*
Constipation	<2*	-	-	-	-	-	-	-
Diarrhea	<2*	-	-	-	-	-	-	-
Gastroenteritis	<2*	-	-	-	-	-	-	-
Glossitis	<2*	-	-	-	-	-	-	-
Loss of taste	<2*	-	-	-	-	-	-	-
Nausea	3*	-	-	-	-	<1	-	≤5†
Stomach discomfort	-	-	-	-	-	<1	-	-
Taste abnormality	-	25	-	1 to 10*	-	-	10 to 30	≤5†
Toothache	<2*	-	-	-	-	-	-	-
Vomiting	<2*	-	-	-	-	-	-	-
Ulcerative stomatitis	<2*	-	-	-	-	-	-	-
Xerostomia	3*	-	-	-	-	-	-	1*
Genitourinary								
Albuminuria	<2*	-	-	-	-	-	-	-
Hematuria	<2*	-	-	-	-	-	-	-
Polyuria	<2*	-	-	-	-	-	-	-
Urinary retention	<1*	-	-	-	-	-	-	-
Urinary tract infection	-	-	-	-	-	-	-	1*
Hepatic								
Alanine aminotransferase increased	<2*	-	-	-	-	-	-	-
Transaminases increased	<1*	-	-	-	-	-	-	-
Musculoskeletal								
Back pain	<2*	-	-	-	-	-	-	≤5†
Extremity pain	<2*	-	-	-	-	-	-	-
Hyperkinesia	<2*	-	-	-	-	-	-	-
Involuntary muscle contractions	<1*	-	-	-	-	-	-	-
Myalgia	≤2*	-	-	-	-	-	-	-
Rheumatoid arthritis	<2*	-	-	-	-	-	-	-
Temporomandibular dislocation	<2*	-	-	-	-	-	-	-
Weakness	-	-	-	-	-	-	-	≤5†
Ocular								
Anterior chamber cells	-	-	-	-	-	<1	-	-

Adverse Events	Azelastine	Bepotastine	Cetirizine	Cromolyn	Epinastine	Lodoxamide	Nedocromil	Olopatadine
Blepharitis	-	-	-	-	-	<1	-	-
Blurred vision	<1*; 1 to 10†	-	-	-	-	1 to 5	-	≤5†
Burning/stinging	30†	-	-	-	1 to 10	15	10 to 30	≤5†
Chemosis	-	-	-	-	-	<1	-	-
Conjunctival injection	-	-	-	✔ †	-	-	-	-
Conjunctivitis	≤2 to 5* 1 to 10†	-	-	-	-	-	1 to 10	≤5†
Corneal abrasion	-	-	-	-	-	<1	-	-
Corneal erosion/ulcer	-	-	-	-	-	<1	-	-
Crystalline deposits	-	-	-	-	-	1 to 5	-	-
Discomfort	-	-	-	-	-	15	-	-
Dry eyes	<1*	-	-	✔ †	-	1 to 5	-	≤5†
Epitheliopathy	-	-	-	-	-	<1	-	-
Eye pain	<2*; 1 to 10†	-	1 to 7	-	-	<1	-	≤5†
Eye redness	-	-	-	-	-	-	1 to 10	-
Eyelid edema	-	-	-	✔ †	-	<1	-	≤5†
Folliculosis	-	-	-	-	1 to 10	-	-	-
Foreign body sensation	-	-	-	-	-	1 to 5	-	≤5†
Hyperemia	-	-	1 to 7	-	1 to 10	1 to 5	-	≤5†
Hypersensitivity reactions	-	-	-	✔ †	-	-	-	-
Irritation	-	2 to 5	-	✔ †	-	-	10 to 30	-
Keratitis	-	-	-	-	-	<1	-	≤5†
Ocular fatigue	-	-	-	-	-	<1	-	-
Photophobia	-	-	-	-	-	-	1 to 10	-
Pruritus	1 to 10†	-	-	✔ †	1 to 10	1 to 5	-	≤5†
Puffy eyes	-	-	-	✔ †	-	-	-	-
Rash	<1*	-	-	-	-	-	-	-
Reduced visual acuity	-	-	1 to 7	-	-	-	-	-
Scales on lid/lash	-	-	-	-	-	<1	-	-
Styes	-	-	-	✔ †	-	-	-	-
Tearing	<2*	-	-	✔ †	-	1 to 5	-	-
Visual disturbances	<1*	-	-	-	-	-	-	-
Warming sensation	-	-	-	-	-	<1	-	-
Respiratory								
Asthma	5*; 1 to 10†	-	-	-	-	-	1 to 10	-
Bronchitis	<2*	-	-	-	-	-	-	-
Bronchospasm	<2*	-	-	-	-	-	-	-
Cold/flu syndrome	2 to 17*;	-	-	-	-	-	-	<10†

Adverse Events	Azelastine	Bepotastine	Cetirizine	Cromolyn	Epinastine	Lodoxamide	Nedocromil	Olopatadine
	1 to 10†							
Cough	11*	-	-	1 to 10*	1 to 3	-	-	1*; ≤5†
Dyspnea	<1*; 1 to 10†	-	-	✔ †	-	-	-	-
Epistaxis	2 to 3*	-	-	<1*	-	-	-	3*
Hoarseness	-	-	-	1 to 10*	-	-	-	-
Laryngitis	<2*	-	-	-	-	-	-	-
Loss of smell	<1*	-	-	-	-	-	-	-
Nasal burning	4*	-	-	>10*	-	-	-	-
Nasal congestion	<2*	-	-	-	-	-	10 to 30	-
Nasal dryness	-	-	-	-	-	<1	-	-
Nasal ulceration	-	-	-	-	-	-	-	9*
Nasopharyngitis	-	2 to 5	-	-	-	-	-	-
Nocturnal dyspnea	<2*	-	-	-	-	-	-	-
Paroxysmal sneezing	3*	-	-	-	-	-	-	-
Pharyngolaryngeal pain	-	-	-	-	-	-	-	2*
Pharyngitis	4*; 1 to 10†	-	-	-	1 to 3	-	-	<10†
Postnasal drip	<2*	-	-	1 to 10*	-	-	-	2*
Rhinitis	2 to 17*; 1 to 10†	-	-	-	1 to 3	-	1 to 10	≤5†
Sinus hypersecretion	<2*	-	-	-	-	-	-	-
Sinusitis	3*	-	-	-	1 to 3	-	-	≤5†
Sneezing	-	-	-	>10*	-	<1	-	-
Throat burning/irritation	<2*	-	-	-	-	-	-	1*
Other								
Allergic reaction	<2*	-	-	-	-	<1	-	-
Anaphylaxis	<1*	-	-	-	-	-	-	-
Application site irritation	<1*	-	-	-	-	-	-	-
Creatine phosphokinase increased	-	-	-	-	-	-	-	1*
Hypersensitivity	-	-	-	-	-	-	-	≤5†
Infection	-	-	-	-	10	-	-	≤5†
Influenza	-	-	-	-	-	-	-	1*
Parosmia	<1*	-	-	-	-	-	-	-
Tolerance	<1*	-	-	-	-	-	-	-
Viral infection	<2*	-	-	-	-	-	-	-
Weight gain	2*	-	-	-	-	-	-	✔ *

✔ Percent not specified.
-Event not reported.
*Nasal formulation.
†Ophthalmic formulation.
‡Astelin®.
§Astepro®.

VII. Dosing and Administration

The usual dosing regimens for the eye, ear, nose, and throat (EENT) antiallergic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the EENT Antiallergic Agents[3-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Azelastine	Allergic conjunctivitis: Solution (ophthalmic): instill 1 drop twice daily Allergic rhinitis (perennial): Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril twice daily Allergic rhinitis (seasonal): Solution (nasal spray): 1 to 2 sprays per nostril twice daily Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril once daily Vasomotor rhinitis: Solution (nasal spray): 2 sprays per nostril twice daily	Allergic conjunctivitis in patients >3 years of age: Solution (ophthalmic): instill 1 drop twice daily Allergic rhinitis (perennial) in patients 6 months to 5 years of age: Solution (nasal spray; Astepro® 0.1%): 1 spray per nostril twice daily Allergic rhinitis (perennial) in patients 6 to 11 years of age: Solution (nasal spray; Astepro® 0.1% or 0.15%): 1 spray per nostril twice daily Allergic rhinitis (perennial) in patients >12 years of age: Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril twice daily Allergic rhinitis (seasonal) in patients 2 to 5 years of age: Solution (nasal spray, 0.1%): 1 spray per nostril twice daily Allergic rhinitis (seasonal) in patients 5 to 11 years of age: Solution (nasal spray): 1 spray per nostril twice daily Allergic rhinitis (seasonal) in patients ≥12 years of age: Solution (nasal spray): 1 to 2 sprays per nostril twice daily Solution (nasal spray; Astepro® 0.15%): 2 sprays per nostril once daily Vasomotor rhinitis in patients >12 years of age: Solution (nasal spray): 2 sprays per nostril twice daily	Solution (nasal spray): 137 µg (0.1%) 205.5 µg (0.15%) Solution (ophthalmic): 0.05%
Bepotastine	Allergic conjunctivitis: Solution: instill 1 drop twice daily	Allergic conjunctivitis in patients ≥2 years of age: Solution: instill 1 drop twice daily	Solution: 1.5%
Cetirizine	Allergic conjunctivitis:	Allergic conjunctivitis in patients	Solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Solution (ophthalmic): instill 1 drop twice daily (approximately 8 hours apart)	≥2 years of age: Solution (ophthalmic): instill 1 drop twice daily (approximately 8 hours apart)	0.24%
Cromolyn	Nasal symptoms of hay fever and other nasal allergies: Solution (nasal spray): 1 spray in each nostril 3 to 4 times per day; maximum, 6 times per day Vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis: Solution (ophthalmic): 1 to 2 drops in each eye 4 to 6 times per day	Nasal symptoms of hay fever and other nasal allergies in patients ≥2 years of age: Solution (nasal spray): 1 spray in each nostril 3 to 4 times per day; maximum, 6 times per day Vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis in patients ≥4years of age: Solution (ophthalmic): 1 to 2 drops in each eye 4 to 6 times per day	Solution (nasal spray): 5.2 mg/spray Solution (ophthalmic): 4%
Epinastine	Allergic conjunctivitis: Solution: instill 1 drop in each eye twice daily	Allergic conjunctivitis in patients ≥2 years of age: Solution: instill 1 drop in each eye twice daily	Solution: 0.05%
Lodoxamide	Vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis: Solution: instill 1 to 2 drops in each eye 4 times daily for up to 3 months	Vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis in patients ≥2 years of age: Solution: instill 1 to 2 drops in each eye 4 times daily for up to 3 months	Solution: 0.1%
Nedocromil	Allergic conjunctivitis: Solution: instill 1 to 2 drops in each eye twice daily	Allergic conjunctivitis in patients ≥3 years of age: Solution: instill 1 to 2 drops in each eye twice daily	Solution: 2%
Olopatadine	Allergic conjunctivitis: Solution (ophthalmic; 0.1%): 1 drop in each eye twice daily at an interval of 6 to 8 hours Solution (ophthalmic; 0.2%): 1 drop in each eye once daily Solution (ophthalmic; 0.7%): 1 drop in each eye once daily Allergic rhinitis (seasonal): Solution (nasal spray): 2 sprays per nostril twice daily	Allergic conjunctivitis in patients ≥2 years of age: Solution (ophthalmic; 0.1%): 1 drop in each eye twice daily at an interval of 6 to 8 hours Solution (ophthalmic; 0.2%): 1 drop in each eye once daily Solution (ophthalmic; 0.7%): 1 drop in each eye once daily Allergic rhinitis (seasonal) in patients 6 to 11 years of age: Solution (nasal spray): 1 spray per nostril twice daily Allergic rhinitis (seasonal) in patients ≥12 years of age: Solution (nasal spray): 2 sprays per nostril twice daily	Solution (nasal spray): 0.6% Solution (ophthalmic): 0.1% 0.2% 0.7%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the eye, ear, nose, and throat (EENT) antiallergic agents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the EENT Antiallergic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Allergic Conjunctivitis				
James et al.[21] (2003) Azelastine in both eyes BID vs cromolyn in both eyes QID vs placebo	DB (azelastine vs placebo), MC, PG, OL (azelastine vs cromolyn) Patients with SAC or rhino-conjunctivitis and symptomatic at time of inclusion	N=144 2 weeks	Primary: Ocular signs and symptoms, global assessment of efficacy and safety Secondary: Not reported	Primary: Both azelastine and cromolyn demonstrated an effect on itching, tearing and conjunctival redness on day three with a sustained improvement on days seven and 14 compared to placebo. A clear response to treatment occurred in 85.4% of azelastine patients and 83.0% of cromolyn patients compared to 56.3% of patients receiving placebo (P=0.005 and P=0.007, respectively). Global assessment of efficacy was at least satisfactory for 90.0% of azelastine patients, 81.3% of cromolyn patients and 66.3% of placebo-treated patients (P values not reported). The most frequent adverse events were transient application site reactions, which tended to disappear with increasing duration of treatment, and, less frequently, taste perversion. Secondary: Not reported
Abelson et al.[22] (2009) Bepotastine 1.0% 1 drop in each eye vs bepotastine 1.5% 1 drop in each eye vs	DB, PC, RCT Patients ≥10 years of age with a history of allergic conjunctivitis	N=107 3 doses	Primary: Patient-assessed ocular itching and investigator-assessed conjunctival hyperemia following CAC Secondary: Not reported	Primary: The differences in mean ocular itching scores between bepotastine 1.0% or 1.5% and the placebo group were significant at all time points measured in the 15-minute onset-of-action and the eight-hour duration-of-action CAC tests (P<0.001 for all). The clinical significance associated with bepotastine 1.5% was similar between the 15-minute and eight-hour CAC tests, whereas the 1.0% solution appeared to be less effective at eight hours compared to 15 minutes after administration. At visit five, the rates of complete relief of ocular itching at the 3-, 5-, and 7-minute time points in the 15-minute onset-of-action CAC test were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				significant with bepotastine 1.0% (44.3, 42.9, and 50.0% of eyes, respectively) and 1.5% (67.2, 48.4, and 53.1%) compared to placebo (1.5, 0, and 1.5%; P≤0.003 for all). Mean conjunctival hyperemia scores were improved with bepotastine 1.0% vs placebo at all three time points in the 15-minute onset-of-action CAC test (P≤ 0.001 for all). With the 1.5% solution, improvement was found at the 7- and 15-minute time points on the 15-minute onset-of-action CAC (P<0.001 and P=0.017, respectively) and at seven minutes on the eight-hour CAC (P=0.01). Secondary: Not reported
Williams et al.[23] (2011) Bepotastine 1% one drop in each eye once vs bepotastine 1.5% one drop in each eye once vs placebo	DB, PC, RCT Patients ≥10 years of age with a history of ocular allergies, positive skin test to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months and positive bilateral CAC reaction within 10 minutes of allergen instillation	N=107 3 weeks (4 visits)	Primary: Patient-assessed ocular itching, physician-assessed conjunctival redness and safety Secondary: Patient-assessed tearing, ciliary and episcleral redness, eyelid swelling, chemosis and mucous discharge	Primary: The mean ocular itching scores in the per protocol population were significantly lower with bepotastine 1 and 1.5% compared to placebo (P<0.001 for both). There was a statistically significant reduction in CAC-induced ocular itching 16 hours following administration of bepotastine 1 and 1.5% compared to placebo in the intention-to-treat populations (P≤0.001 for both). In the per protocol population, 40.0% of patients receiving bepotastine 1.5% experienced a two-unit reduction in ocular itching at one or more CAC time points compared to 34.3% of those in the bepotastine 1% group and 5.9% in the placebo group (P<0.05 for both compared to placebo). Of patients with severe itching, a two-unit reduction in ocular itching score at one or more time points occurred in 8.7% of the placebo group compared to 37.5 and 43.5% of patients receiving bepotastine 1% (P=0.001) and 1.5% (P=0.008), respectively. Bepotastine 1% was significantly more effective compared to placebo for reducing mean conjunctival redness seven minutes following the 16-hour CAC test (P≤0.012). There were no clinically significant differences (one unit or more change) in conjunctival redness between bepotastine (1 or 1.5%) and placebo at any time point 16 hours after dosing.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Compared to placebo, bepotastine 1 and 1.5% were associated with statistically significant reductions in eyes with tearing (51.2 and 85.6 vs 27.5%, respectively; P<0.05 for both compared to placebo). Improvements in tearing were significantly greater in patients receiving bepotastine 1.5% compared to those treated with bepotastine 1% (P=0.0046).
Macejko et al.[24] (2010) Bepotastine 1.0% 1 drop in each eye vs bepotastine 1.5% 1 drop in each eye vs placebo	DB, MC, PC, RCT Patients ≥10 years of age with a positive allergen skin test	N=130 Single dose	Primary: Ocular itching and conjunctival hyperemia following CAC Secondary: Not reported	Primary: Bepotastine (1.0 and 1.5%) demonstrated a reduction in ocular itching (P<0.0001) compared to placebo (within three minutes after a CAC and at every other time point after a CAC performed 15 minutes or eight hours after test agent instillation). Bepotastine 1.5% demonstrated a slightly higher degree of reduced ocular itching than seen for the 1.0% formulation. An improvement in conjunctival redness was observed at most time points at the onset of action CAC test for both bepotastine formulations (P<0.0125). There was less conjunctival redness improvement seen at the eight- and 16-hour duration-of-action CAC tests. Secondary: Not reported
Torkildsen et al.[25] (2010) Bepotastine 1.5% 1 drop in each eye vs placebo	DB, PC, RCT Patients ≥10 years of age with a history of allergic conjunctivitis	N=70 Single dose	Primary: Non-ocular effectiveness following CAC Secondary: Not reported	Primary: Treatment with bepotastine led to a significant reduction in rhinorrhea and nasal congestion compared to placebo at all time points (P≤0.01). There was a significant reduction in nasal pruritus and ear or palate pruritus with bepotastine (P≤0.025 for visits 3 and 4 and P≤0.05 for visit 5) compared to placebo. The summed NOCS score was improved with bepotastine compared to placebo at most time points for at least 16 hours after dosing (P≤0.01). Secondary: Not reported
McCabe et al.[26] (2012)	AC, RCT, SB, XO Patients ≥18 years	N=30 2 weeks	Primary: Relief of ocular itch, itchy/runny	Primary: There was a similar improvement in the relief of morning ocular itch between patients receiving bepotastine and olopatadine (P value not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bepotastine 1.5% 1 drop in affected eye(s) BID vs olopatadine 0.2% 1 drop in affected eye(s) QD	of age with allergic conjunctivitis and no concurrent unrelated ocular diseases and no plans to undergo ocular surgery during the study period		nose, ocular allergy symptoms, eye drop comfort and patient preference Secondary: Not reported	reported). Patients treated with bepotastine reported a significantly greater relief in evening ocular itch compared to patients receiving olopatadine (P=0.011). Olopatadine was significantly more effective at relieving ocular itching in the morning compared to the evening (P<0.0001), whereas bepotastine was equally effective at both time points. For the all-day relief of ocular itching, significantly more patients favored treatment with bepotastine compared to treatment with olopatadine (63.3 vs 36.7%; P=0.04). Bepotastine was significantly more effective at relieving morning and evening itchy/runny nose compared to olopatadine (P=0.0001). Bepotastine provided significantly more itchy/runny nose relief in the evening compared to the morning (P<0.035), whereas olopatadine provided a similar relief between morning and evening. A significantly greater proportion of patients preferred bepotastine compared to olopatadine for all-day relief of itchy/runny nose (66.7 vs 33.3%; P=0.01). A greater proportion of patients preferred bepotastine with regard to eye drop comfort compared to olopatadine (56.7 vs 43.3%; P value not reported). Treatment with bepotastine was significantly more effective for relief of morning and evening ocular allergy symptoms (P=0.032 and P<0.0001, respectively) compared to treatment with olopatadine. Bepotastine was equally efficacious for improving ocular allergy symptoms in the morning and evening, whereas olopatadine was significantly more effective in the morning (P<0.001). Significantly more patients preferred bepotastine for the overall treatment of allergic conjunctivitis compared to olopatadine (66.7 vs 33.3%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.01). Secondary: Not reported
Meier et al.[27] (2018) Cetirizine 0.24% vs placebo (vehicle) 1 to 2 drops bilaterally at visit 3 and 4	Two DM, PC, PG, RCT Patients ≥10 years of age, must have had a positive bilateral CAC reaction within 10 minutes of instillation of the last titration of allergen at visit 1 and at had a positive bilateral CAC reaction for at least two of the three time points at visit 2	N=100 (Study 1) and 101 (Study 2) 5 weeks	Primary: Ocular itching and conjunctival redness 15 minutes and 8 hours post-treatment, post-CAC Secondary: Ciliary and episcleral redness, chemosis, eyelid swelling, tearing, rhinorrhea, nasal pruritus, ear or palatal pruritus, nasal congestion, and composite score of presence or absence of at least one nasal symptom	Primary: Cetirizine ophthalmic solution 0.24% was effective at preventing ocular itching at 15 minutes post-treatment instillation. Post-CAC mean treatment differences were in favor of cetirizine ophthalmic solution 0.24% and were significantly lower than vehicle at 3, 5, and 7 minutes for both studies 15 minutes after treatment instillation (P<0.0001 for each time point). The cetirizine ophthalmic solution 0.24% treatment group had mean ocular itching score of at least 1 U lower than the vehicle treatment 15 minutes after study medication instillation at 3, 5, and 7 minutes post-CAC. The mean ocular itching score in the cetirizine ophthalmic solution 0.24% group was 1.0 compared to a mean score of 2.38 in the vehicle group, 15 minutes after treatment instillation and 3 minutes post-CAC, in Study 1. Study 2 results and treatment differences were confirmatory of strong ocular itching efficacy at 15 minutes post-treatment instillation. The greatest difference observed between cetirizine 0.24% ophthalmic solution treatment group and vehicle treatment group was 1.53 U at 3 minutes post-CAC. Here, the mean ocular itching score was 2.54 in the vehicle group compared to 1.01 in the cetirizine ophthalmic solution 0.24% group Cetirizine ophthalmic solution 0.24% demonstrated persistent efficacy at 8 hours post-treatment instillation. The cetirizine ophthalmic solution 0.24% group had significantly lower mean itching scores than vehicle treatment as early as 3 minutes post-CAC (P<0.0001). The difference between the cetirizine ophthalmic solution 0.24% group and vehicle was near 1 U and significantly different at all 8 hours post-treatment instillation post-CAC time points (P<0.0001 for each time point). The minimum difference between the groups was -0.84 U (Study 2, 7 minutes post-CAC), and the maximum difference in itching score was from -0.99 U (Study 1, 7 minutes post-CAC) compared to vehicle. Treatment differences were in favor of the cetirizine ophthalmic solution 0.24% group compared to vehicle at all post-CAC time points 15 minutes and 8 hours post-treatment instillation.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Across all 15 minutes post-treatment post-CAC time points, the mean ciliary redness score was significantly lower in the cetirizine group compared to vehicle by 0.26 U (Study 1, P=0.0007) and 0.30 U (Study 2, P=0.0337). Eight hours post-treatment instillation, ciliary redness continued to be lower in the cetirizine treatment group across all post-CAC time points in both studies. Chemosis was significantly lower across all post-CAC time points, at both 15 minutes and 8 hours post-treatment in both Study 1 and Study 2 (P<0.05 across all post-CAC time points) ranging from a difference of 0.17 to 0.38. Eyelid swelling was also significantly improved across all post-CAC time points at both 15 minutes and 8 hours post-treatment, in both studies (P<0.05 in Study 1 and P<0.0001 in Study 2). In Study 1, a mean difference of 0.30 U at 15 minutes post-treatment and 0.40 U at 8 hours post-treatment was observed. Significant improvement was observed in subject tearing. Subjects reported tearing pre-CAC and then again at 7, 15, and 20 minutes post-CAC both 15 minutes and 8 hours post-treatment. Tearing was significantly lower at 15 minutes post-treatment with cetirizine in Study 1 (0.30 U, P=0.0191) and Study 2 (0.50 U, P=0.0004) across all post-CAC time points. The mean score for every nasal symptom such as rhinorrhea, nasal pruritus, ear or palatal pruritus and nasal congestion, was in favor of the cetirizine ophthalmic solution 0.24% group across all three time points. The most notable superiority in the cetirizine group was rhinorrhea. Rhinorrhea was significantly lower by 0.4 to 0.7 U across all post-CAC time points, at both 15 minutes post-treatment and 8 hours post-treatment (P<0.05). Nasal pruritus was significantly improved across all post-CAC time points at 8 hours post-treatment in Study 1 (P=0.0184) and 15 minutes post-treatment in Study 2 (P=0.0043). Ear or palatal pruritus was significantly improved in Study 2, where the mean score was significantly lower in the cetirizine ophthalmic solution 0.24% group than in the vehicle by 0.5 U (P=0.0025) at 15 minutes post-treatment and 0.6 U (P<0.0001) at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				8 hours post-treatment. Nasal congestion was significantly improved in the cetirizine ophthalmic solution 0.24% group compared to vehicle across all treatment groups at 8 hours post-treatment (-0.4 U, P=0.0209) in Study 1 and at both 15 minutes post-treatment (-0.7 U, P=0.0003) and 8 hours post-treatment (-0.4 U, P=0.0020) in Study 2.
Malhotra et al.[28] (2019) Cetirizine 0.24% BID (Study 1) or TID (Study 2) vs placebo	Two DM, MC, PC, PG, RCT Adult and pediatric (≥2 to ≤18 years of age) with a history or family history of atopic disease, including allergic conjunctivitis with the ability to self-administer eye drops or have a caregiver, legal guardian or school healthcare provider due so, and a calculated visual acuity of 0.3 logMAR or better in each eye as measured using an ETDRS chart	N=512 (Study 1) and 516 (Study 2) 6 weeks	Primary; Safety parameters (IOP, dilated ophthalmoscopy, ECC evaluations among participating subjects, physical examination, and vital signs) Secondary: Adverse events and tolerability	Primary: In both study 1 and 2, no clinically or statistically significant differences in safety parameters were observed between the cetirizine and vehicle groups, with the exception of AEs. Secondary: In study 1, ocular TEAEs were reported by 121 subjects (23.6%) with 141 ocular TEAE incidences. The prevalence of ocular TEAEs among the cetirizine group (22.9%) was lower than that of vehicle group (25.1%). Of the 91 ocular TEAEs reported by 78 subjects in the cetirizine group, 88 were classified as mild and three moderate (Table 2). The most common ocular TEAEs (≥1%) in the cetirizine group were conjunctival hyperemia, instillation site pain, and ocular hyperemia, collectively accounting for 61 of 91 ocular disorders in the cetirizine group. In study 2, 37 subjects (7.2%) reported 45 ocular TEAEs. The prevalence of ocular TEAEs among subjects in the cetirizine group (6.7%) was lower than in the vehicle group (8.1%). In both the groups, the majority of the TEAEs were classified as mild. In the cetirizine group, the ocular TEAEs occurring in ≥1% of subjects were reduced visual acuity, conjunctival hyperemia, and instillation site pain
Greiner et al.[29] (abstract) (2002) Cromolyn 4% in 1 eye QID for 2 weeks, followed by 1 drop once at the final visit	AC, SB Patients who responded to the conjunctival provocation test, study used CAC model	N=56 2 weeks	Primary: Ocular itching, tearing and redness following CAC, comfort and safety Secondary: Not reported	Primary: At the 15-minute and four-hour CAC tests, ketotifen was significantly more effective than cromolyn in preventing itching (P<0.001) and redness (P≤0.001) at most assessments. Tearing scores were higher in patients receiving cromolyn compared to patients receiving ketotifen. Patients reported greater comfort in the eyes treated with ketotifen compared to cromolyn; however, the difference was not statistically significant (P=0.066). The most common adverse event associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo other eye QID for 2 weeks, followed by ketotifen 0.025% 1 drop once at the final visit				cromolyn was burning/stinging. A single dose of ketotifen was more effective than a two-week regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the CAC model. Secondary: Not reported
Figus et al.[30] (2010) Cromolyn sodium 4% and chlorpheniramine 0.2% BID vs diclofenac 0.1% BID vs epinastine 0.05% BID vs fluorometholone 0.2% BID vs ketotifen 0.05% BID	MC, RCT, SB Patients ≥18 years of age with allergic conjunctivitis	N=240 1 month	Primary: Percentage of patients achieving at least a "small" or "good" improvement of signs and symptoms Secondary: Not reported	Primary: Naphazoline and antazoline induced significantly higher discomfort compared to the other study treatments (P<0.0001). Ketotifen was associated with the least discomfort. All study treatments induced a significant reduction in mean scores for both signs and symptoms compared to baseline (P<0.0001). At the end of the study, the mean score for signs was similar in the study groups (P>0.5). Diclofenac and naphazoline and antazoline showed less efficacy in decreasing symptoms compared to the other treatments (P<0.05). At the end of the study, good improvement of symptoms was obtained in at least 70% of patients by epinastine, ketotifen, fluorometholone, and olopatadine, whereas a 70% improvement in signs was obtained only by fluorometholone and ketotifen. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levocabastine 0.05% BID vs naphazoline and antazoline 0.25-5 mg/mL BID vs olopatadine 0.1% BID				
D'Arienzo et al.[31] (2002) Emedastine 0.05% in 1 eye and placebo in the contralateral eye vs ketotifen 0.025% in 1 eye and placebo in the contralateral eye vs emedastine 0.05% in 1 eye and ketotifen 0.025% in the contralateral eye	DB, PC, RCT Patients with allergic conjunctivitis	N=45 Single dose	Primary: Signs and symptoms following CAC Secondary: Not reported	Primary: Treatment with emedastine and ketotifen resulted in significant reductions in raw mean itching scores at all time points compared to placebo ($P<0.05$). This was seen at both the five- and 15-minute challenges. There were no significant differences in itching scores between emedastine and ketotifen at either the five- or 15-minute challenge. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Orfeo et al.[32] (abstract) (2002) Emedastine 0.05% in 1 eye once and placebo other eye once vs nedocromil 2% in 1 eye once and placebo other eye once Each patient received both study drugs on two different visits.	AC, DB, PC, RCT, XO Patients with a history of allergic conjunctivitis, study used CAC model	N=30 Duration not reported (3 visits)	Primary: Ocular itching and redness at three, 10 and 20 minutes following CAC Secondary: Not reported	Primary: Emedastine and nedocromil were significantly more effective compared to placebo in controlling ocular itching and redness following CAC test (P<0.01). Emedastine was significantly more effective in alleviating redness and itching at three and 10 minutes after the allergen CAC test compared to nedocromil (P<0.01). Secondary: Not reported
Fujishima et al.[33] (2014) Epinastine 0.05% vs olopatadine 0.1% *and* Epinastine 0.05% vs placebo	AC, DB, PC, RCT Adults with a history of seasonal allergic conjunctivitis and cedar pollen-specific IgE who were asymptomatic before the allergen challenge, study used CAC model (cedar pollen)	N=87 Duration not reported (7 visits)	Primary: Ocular itching score and conjunctival hyperemia score at 3 specified time points after CAC (ocular itching at 3, 5, and 10 minutes; conjunctival hyperemia at 5, 10, and 20 minutes) Secondary: Safety	*Epinastine vs placebo (superiority study)* Primary: The mean ocular itching scores (mean ± SE) for the 3 time points after allergen challenge at 4 hours were 0.4 ± 0.1 and 1.7 ± 0.1 for epinastine and placebo, respectively (P<0.001). The mean conjunctival hyperemia scores (mean ± SE) for the 3 time points after the allergen challenge at 4 hours were 2.7 ± 0.1 and 4.1 ± 0.2 for epinastine and placebo, respectively (P<0.001). *Epinastine vs olopatadine (noninferiority study)* Primary: Noninferiority of epinastine to olopatadine with respect to the mean ocular itching score and conjunctival hyperemia score was verified. *Data from all patients contributed to safety outcomes* Secondary: Adverse events were reported in 5 of the 87 subjects included in the safety

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				analysis set (nasopharyngitis, urticaria, wound formation, oropharyngeal discomfort, and conjunctivitis). All events were considered unrelated to the study drug.
Torkildsen et al.[34] (2008) Epinastine 0.05% vs azelastine 0.05% vs ketotifen 0.025% Patients were randomized to receive a single drop of epinastine in 1 eye and either azelastine or ketotifen in the other eye (contralateral dosing).	DB, RCT, XO Patients ≥18 years of age with allergic conjunctivitis	N=40 Single dose	Primary: Ocular comfort Secondary: Not reported	Primary: The mean comfort score was significantly lower (indicating more comfort) with epinastine than azelastine at 0.5, one, two, and five minutes after instillation (P<0.001, P<0.001, P=0.001, and P=0.019, respectively) and compared to ketotifen immediately after instillation (P=0.014). The mean comfort score was significantly lower with ketotifen compared to azelastine at 0.5, one, and two minutes (P=0.001, P=0.023, and P=0.028). With epinastine, 85% of descriptors were positive and 5% were negative; with azelastine, 41 and 34%, respectively; with ketotifen, 55 and 28%. Neutral descriptors were used for epinastine, azelastine, and ketotifen in 10, 25, and 17% of cases, respectively. There were no significant differences between treatments in fluorescein staining scores and OPI values. Secondary: Not reported
Greiner et al.[35] (2002) Ketotifen 0.025% as a single dose vs cromolyn sodium 4% QID for 2 weeks (as a	AC, RCT, SB Patients ≥18 years of age with a history of allergy to environmental allergens not currently in season	N=56 Single dose	Primary: Signs and symptoms following CAC Secondary: Not reported	Primary: Ketotifen was more effective than cromolyn in the prevention of itching at the 7-minute evaluation (P<0.001). Ketotifen was more effective than cromolyn in preventing redness (ciliary, conjunctival and episcleral) at both seven and 15 minutes (P<0.001). Following the 15 minute challenge, cromolyn-treated eyes exhibited more tearing than ketotifen-treated eyes at seven minutes (28 vs 9%) and 15 minutes (13 vs 4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loading dose) One eye was treated with the study drug and the other eye was treated with placebo.				Following the four-hour challenge, more tearing occurred in cromolyn-treated than in ketotifen-treated eyes at seven minutes (13 vs 6%) and 15 minutes (15 vs 9%). Secondary: Not reported
Greiner et al.[36] (2003) Ketotifen 0.025% in 1 eye and nedocromil 2% in the contralateral eye vs ketotifen 0.025% in 1 eye and artificial tears in the contralateral eye vs nedocromil 2% in 1 eye and artificial tears in the contralateral eye	AC, DB, PC, RCT Patients ≥10 years of age with a history of allergic hypersensitivity	N=59 Single dose	Primary: Ocular itching following CAC Secondary: Not reported	Primary: Peak itching occurred in the range of four to ten minutes after the allergen challenge. The itching response diminished after ten minutes. At both five minutes and 12 hours after medication administration, placebo and nedocromil exhibited similar responses. Ketotifen controlled itching better than both placebo and nedocromil at every time point after 30 seconds post-challenge in the five-minute data and every time point after 90 seconds post-challenge in the 12-hour data. These treatment differences were significant from two to 18 minutes in the 5-minute data ($P<0.05$ for all) and from three to 12 minutes in the 12-hour data ($P<0.05$ for all). Onset of action: The comparison of ketotifen-treated eyes with those that received placebo showed a significant difference from two through 19.5 minutes post-challenge ($P<0.05$). Scores of nedocromil-treated eyes were not difference from those that received placebo at any time point. Ketotifen mean itching scores were significantly lower than nedocromil mean itching scores from two to 18 minutes post-challenge ($P<0.05$). Duration of action (12-hour data): The comparison of ketotifen-treated eyes with those that received placebo showed a significant difference from three to 12 minutes post-challenge ($P<0.05$). Scores of nedocromil-treated eyes were not different from those that received placebo at any time point. Ketotifen mean itching scores were significantly lower than nedocromil mean itching scores from 2.5 to 14 minutes post-challenge ($P<0.05$). Ketotifen-treated eyes were more comfortable than nedocromil-treated eyes at all time points. The comfort differences between ketotifen and nedocromil were significant at one, two, five, and ten minutes after eye drop instillation ($P<0.05$). Ketotifen showed no difference from placebo in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				terms of comfort. The percentage of the comfortable responses was 52% for both ketotifen and placebo and 37% for nedocromil. Immediately after instillation, unfavorable terms (burning, stinging, or irritating) were used to describe nedocromil in 48% of instances, compared to 26 and 12% for ketotifen and placebo, respectively. Five minutes after the medication was instilled, comfortable was the most common descriptive term for ketotifen and placebo (72 and 49%, respectively, compared to 27% for nedocromil); stinging was the most common descriptive term for nedocromil (31%). The proportion of unfavorable descriptive terms (burning, stinging, or irritating) was 6% for ketotifen, 12% for placebo, and 55% for nedocromil. The patient satisfaction rates were 60% with ketotifen treatment, 21% with nedocromil treatment, and 19% with placebo. Secondary: Not reported
Avunduk et al.[37] (2005) Ketotifen 0.025% 2 drops in each eye BID vs olopatadine 0.1% 2 drops in each eye BID vs artificial tears 2 drops in each eye BID	DB, RCT Patients ≥18 years of age with a history of seasonal allergic conjunctivitis over the previous 2 years, including moderate to severe ocular itching (severity based on patient's history); and had at least 1 of the following bilateral signs of at least moderate severity: conjunctival	N=39 30 days	Primary: Clinical scores (itching, tearing, redness, eyelid, swelling, and chemosis) Secondary: Not reported	Primary: In the ketotifen group, the mean itching scores were significantly lower on days 15 and 30 compared to the mean score obtained on day 0 (both, P=0.001). In the olopatadine group, the mean itching scores were significantly lower on days 15 and 30 compared to that on day 0 (P=0.016 and P=0.017, respectively). On days 15 and 30, the mean itching scores in the ketotifen-treated patients and those who received olopatadine were significantly lower compared to those in the artificial tears group (ketotifen; P=0.042 and P=0.028, respectively; olopatadine; P=0.032 and P=0.026, respectively). There was no significant difference between ketotifen and olopatadine groups at any time point. Mean tearing scores in the ketotifen group were significantly lower on days 15 and 30 compared to the baseline score (P=0.008 and P=0.014, respectively). The mean tearing scores were significantly lower in the ketotifen-treated patients compared to those in the artificial tears group on days 15 and 30 (P=0.017 and P=0.02, respectively). In the olopatadine group, the mean tearing scores were significantly lower on days 15 and 30

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	redness, conjunctival chemosis, and eyelid swelling			compared to that on day 0 (P=0.018 and P=0.016, respectively). Olopatadine-treated patients had a significantly lower mean tearing score compared to that in the artificial tears group on day 15 (P=0.038). There was no significant difference between the ketotifen- and olopatadine-treated patients in mean tearing scores at any time point. No significant within-group or between-group differences were found in terms of mean scores for redness, eyelid swelling, or chemosis at any time point. Secondary: Not reported
Abelson et al.[38] (2007) Olopatadine 0.1% 1 drop in 1 eye every eight hours for two doses vs olopatadine 0.2% 1 drop in 1 eye once vs placebo Study medications were administered contralaterally.	DB, PC, RCT Patients who responded to the ocular allergen challenge, study used CAC model	N=23 3 weeks (3 visits)	Primary: Ocular itching at three, five and seven minutes following CAC (allergen administered 24 hours after study drug instilled) and safety Secondary: Not reported	Primary: At the 24-hour CAC test, olopatadine 0.1 and 0.2% significantly reduced itching scores compared to placebo (P=0.002 and P=0.0007, respectively). There were no statistically significant differences between patients receiving olopatadine 0.1 and 0.2% (P=0.081). Olopatadine 0.1 and 0.2% were both found to be safe and well tolerated as used in this study. No adverse events were reported. Secondary: Not reported
Spangler et al.[39] (2001) Olopatadine 0.1% in 1 eye and	DB, MC, RCT Patients with allergic conjunctivitis	N=111 Single dose	Primary: Ocular itching following CAC Secondary:	Primary: Olopatadine and azelastine were both significantly more effective than placebo at reducing itching post-challenge. Olopatadine was significantly more effective than azelastine in preventing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
artificial tears in the contralateral eye vs azelastine 0.05% in 1 eye and artificial tears in the contralateral eye vs olopatadine 0.1% in 1 eye and azelastine 0.05% in the contralateral eye			Not reported	itching at 3.5 minutes through 20 minutes post challenge (P<0.05). Secondary: Not reported
McLaurin et al.[40] (2015) Olopatadine 0.77% vs olopatadine 0.2% vs olopatadine 0.1% vs vehicle	DB, MC, RCT Patients ≥18 years of age with a history of allergic conjunctivitis and a confirmed positive bilateral CAC response	N=345 5 weeks	Primary: Patient-assessed ocular itching Secondary: Investigator-assessed conjunctival redness and total redness	Primary: Olopatadine 0.77% was more effective than the vehicle for alleviating ocular itching at all three post-CAC time points at onset and 24 hours (difference in means, –0.9 to –1.5; P<0.0001 for all comparisons). A difference in means ≥1 unit compared with the vehicle is considered clinically relevant by the Food and Drug Administration in a CAC study. The difference in means was >1 unit at majority of post-CAC time points (at all three time points for onset and at two of three time points for 24-hour). Furthermore, at the 24-hour visit, olopatadine 0.77% demonstrated more improvement in ocular itching to olopatadine 0.2% at three and five minutes after CAC (difference in means, –0.3 to –0.3; P<0.05), and to olopatadine 0.1% at all three post-CAC time points (difference in means, –0.4 to –0.5; P<0.05). Secondary: Olopatadine 0.77% significantly improved conjunctival redness and total redness compared with all comparators at the onset of action (differences in means, –0.3 to –0.6 and –0.8 to –2.0, respectively; both P<0.05). No

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				safety concerns for olopatadine 0.77% were identified.
Katelaris et al.[41] (2002) Olopatadine 0.1% BID vs cromolyn sodium 2% QID	MC, RCT Patients with seasonal allergic conjunctivitis	N=185 6 weeks	Primary: Ocular itching and conjunctival redness Secondary: Not reported	Primary: By day 42, olopatadine was significantly more effective in reducing itching and redness compared to cromolyn sodium (P<0.05). Secondary: Not reported
Liu et al.[42] (2017) Olopatadine hydrochloride 0.1% (Patanol®) BID vs emedastine difumarate 0.05% (Emadine®) BID vs or loteprednol etabonate 0.5% (Lotemax®) 4 times a day vs vehicle 3 times a day (Refresh Plus®)	PC, PRO, RCT, SB Patients 5 to 10 years of age with seasonal allergic conjunctivitis	N=80 15 days	Primary: Changes in symptoms Secondary: Not reported	Primary: After one week, changes in ocular itching, blinking of eyes, and photophobia were statistically significant (P<0.05) between the study groups and the placebo group. There were no statistically significant differences among the treatment groups (P>0.05). After two weeks of treatment, the changes in ocular itching, blinking of eyes, and photophobia were statistically significant between the study groups and the vehicle group (P<0.05), and there were no statistically significant differences among the treatment groups (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lanier et al.[43] (2004) Olopatadine 0.1% in 1 eye and epinastine 0.05% in the contralateral eye vs olopatadine 0.1% in 1 eye and placebo in the contralateral eye vs epinastine 0.05% in 1 eye and placebo in the contralateral eye	DB, RCT Patients with allergic conjunctivitis	N=66 Single dose	Primary: Itching and conjunctival redness following CAC Secondary: Not reported	Primary: Olopatadine-treated eyes showed significantly lower mean itching and conjunctival redness scores than epinastine-treated eyes (P=0.003 and P<0.001, respectively). Olopatadine-treated eyes showed significantly less chemosis (P<0.001), ciliary redness (P<0.001), and episcleral redness (P<0.001) than epinastine-treated eyes. Secondary: Not reported
Mah et al.[44] (2007) Olopatadine 0.2% in 1 eye and epinastine 0.05% in the contralateral eye vs olopatadine 0.2% in 1 eye and placebo in the contralateral eye	DB, PC, RCT Patients with allergic conjunctivitis	N=92 Single dose	Primary: Efficacy and comfort following CAC Secondary: Not reported	Primary: Both active treatments were more effective than placebo at preventing ocular itching at all assessment time points (P<0.001 for both treatments). Olopatadine 0.2% was associated with significantly lower mean ocular itching scores in comparison to epinastine 0.05% at five minutes (P=0.024) and seven minutes (P=0.003). There was no significant difference in mean itching scores at three minute post-challenge. Compared to placebo, epinastine 0.05% demonstrated lower mean ciliary redness scores at seven minutes (P<0.002). Olopatadine 0.2% demonstrated lower mean redness scores for all three vessel beds at all assessment time points (ciliary; P<0.001, conjunctival; P<0.0012, and episcleral; P<0.001). Olopatadine 0.2% was associated with lower mean redness scores in comparison to epinastine 0.05% in all three vessel beds at all assessment time points (ciliary; P≤0.013, conjunctival; P≤0.015, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs epinastine 0.05% in 1 eye and placebo in the contralateral eye vs placebo				episcleral; P≤0.006). When paired with placebo-treated eyes, olopatadine 0.2%-treated eyes were significantly more comfortable (P<0.05) at two and five minutes post-dose. The differences between mean comfort scores for the epinastine 0.05% and placebo-paired eyes were not significantly different. In the group of patients receiving contralateral olopatadine 0.2% and epinastine 0.05%, comfort scores for olopatadine 0.2%-treated eyes were statistically better at the one minute time point (P=0.030). There were no significant differences in eye drop comfort scores at two and five minutes post-instillation. Secondary: Not reported
Aguilar et al.[45] (2000) Olopatadine 0.1% 1 drop every 12 hours vs ketotifen 0.05% 1 drop every 12 hours	OL Patients 19 to 68 years of age with a history of allergy who were showing signs/symptoms of allergic conjunctivitis	N=80 14 days	Primary: Signs and symptoms of allergic conjunctivitis Secondary: Not reported	Primary: In the olopatadine group, 42.5 to 62.5% of patients showed improvement in signs and symptoms assessed between 0 and 30 minutes after initial instillation of the study medication; however, there was no improvement in mucous discharge. At 48 hours, improvements in every evaluated parameter were observed in 57.5 to 75% of patients. After seven days of treatment, complete control of all evaluated signs and symptoms was achieved in 80 to 87.5% of patients. In the ketotifen group, 20.0 to 47.5% of patients showed improvement in the signs and symptoms assessed between 0 and 30 minutes after initial instillation of the study medication; however, there was no improvement in mucous discharge. At 48 hours, improvements in every evaluated parameter were observed in 27.5 to 48% of patients. After seven days of treatment, 60 to 75% of patients showed improvements. With continued treatment through day 14, control of all signs and symptoms evaluated was observed in 67.5 to 75% of patients. Secondary: Not reported
Berdy et al.[46] (2000)	DB, RCT Patients with	N=32 Single dose	Primary: Ocular itching and patient satisfaction	Primary: Olopatadine was significantly more effective than ketotifen at all time points (three, five, and 10 minutes) in reducing the itching induced by the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Olopatadine 0.1% vs ketotifen 0.025%	allergic conjunctivitis		following CAC Secondary: Not reported	CAC (P<0.05). The mean efficacy scores for olopatadine were significantly higher than those for ketotifen at three and five minutes post-challenge (P<0.05). Olopatadine-treated eyes were rated as significantly more comfortable than those treated with ketotifen (P<0.05). Of the patients who had a preference, 73% identified olopatadine and 27% were more satisfied with ketotifen and identified ketotifen as the more tolerable formulation. Secondary: Not reported
Ganz et al.[47] (2003) Olopatadine 0.1% BID vs ketotifen 0.025% BID	AC, DB, PG, RCT Patients ≥12 years of age with seasonal allergic conjunctivitis	N=66 3 weeks	Primary: Responder rates Secondary: patient and investigator assessments of global efficacy, as well as signs and symptoms	Primary: More patients responded to treatment with ketotifen than to olopatadine, according to both patient and investigator assessments. The difference between groups was significant for the investigator evaluation at visit two (P<0.0001) and for the patient (P=0.0001) and investigator (P<0.0001) evaluations at visit three. Secondary: The patient-assessed mean global efficacy scores were significantly lower with ketotifen than olopatadine at day five (P=0.03) and day 21 (P=0.0005). The investigator-assessed mean global efficacy scores were significantly lower with ketotifen than olopatadine at day five (P=0.001) and day 21 (P<0.0001). The ketotifen group had significantly lower scores for conjunctival hyperemia at day five (right; P=0.048, left; P=0.032), and day 21 (right; P=0.003, left; P=0.003) compared to olopatadine. The ketotifen group had significantly lower scores for itching at day five (right; P=0.007, left; P=0.008), and day 21 (right; P<0.0001, left; P<0.0001) compared to olopatadine. There was no significant difference in tearing among the treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				at day five or day 21. Between baseline and visit two (days five to eight), treatment with ketotifen significantly decreased conjunctival hyperemia, itching, and tearing, along with total signs and symptoms; treatment with olopatadine significantly decreased itching, tearing, and total symptom scores. At all visits, ketotifen and olopatadine were rated between 0 (comfortable, no sensation) and one (mild, slightly perceptible sensation). No significant differences were found between treatments.
Borazan et al.[48] (2009) Olopatadine 0.1% BID vs ketotifen 0.025% BID vs epinastine 0.05% BID vs emedastine 0.05% BID vs fluorometholone 0.1% BID	DB, PC, RCT Patients with seasonal allergic conjunctivitis	N=100 2 weeks	Primary: Patient-assessed signs and symptoms Secondary: Not reported	Primary: Scores for ocular itching, conjunctival redness, tearing, chemosis and eyelid swelling were significantly improved in drug-treated eyes compared to placebo-treated eyes in all treatment groups (P<0.001). Ocular itching and conjunctival redness were significantly less improved in eyes in the fluorometholone group compared to all other groups. Although scores for tearing, chemosis and eyelid swelling showed a clinical improvement in all groups, there were no significant between-group differences. There were no significant differences in itching and tearing scores between days seven and 14 in the placebo-treated eyes. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
One eye was treated with study drug and the other eye was treated with placebo.				
Leonardi et al.[49] (2004) Olopatadine 0.1% 2 drops per eye per day vs ketotifen 0.025% 2 drops per eye per day Patients were required to use both bottles during the study, but were allowed to use their own discretion to determine the number of times required to use each medication to determine preference.	DB, MC Patients with seasonal or perennial allergic conjunctivitis	N=100 4 weeks	Primary: Patient preference Secondary: Not reported	Primary: Patients reported a significant preference for using olopatadine, with 81% indicating this preference, 17% preferring ketotifen, and 2% indicating no preference (P<0.0001). When asked which medication provided better relief of signs and symptoms of ocular allergy, such as itching, redness, and lid swelling, 81% of patients chose olopatadine, 19% selected ketotifen, and zero indicated no preference (P<0.0001). A significant percentage of patients selected olopatadine as more comfortable (81%) compared to ketotifen (18%; P<0.0001); 1% indicated no preference. In response to the question regarding the drop patients would request if visiting the doctor's office during allergy season, 81% would request olopatadine, 18% ketotifen, and 1% had no preference. The difference between olopatadine and ketotifen was significant (P<0.0001). Secondary: Not reported
Butrus et al.[50] (2000) Olopatadine 0.1% as a single dose	DB, RCT Patients with allergic conjunctivitis	N=52 Single dose	Primary: Ocular itching and comfort following CAC	Primary: Olopatadine was more efficacious than nedocromil at reducing itching at all time points (three, five, 10 minutes; P<0.0001). Olopatadine was more comfortable than nedocromil (P=0.034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nedocromil 2% administered for 2 weeks (loading dose)			Secondary: Not reported	Secondary: Not reported
Alexander et al.[51] (2000) Olopatadine 0.1% 1 drop into each eye BID for 1 week vs nedocromil 2% 1 drop into each eye BID for 1 week	OL, RCT, XO Patients ≥7 years of age with perennial allergic conjunctivitis and use of olopatadine within the previous 12 months	N=28 2 weeks	Primary: Patient satisfaction, severity of ocular symptoms, clinical signs, quality of life, and global assessments of effectiveness Secondary: Not reported	Primary: Mean symptom scores for seven ocular symptoms were comparable with nedocromil and olopatadine, except that light sensitivity was significantly lower with nedocromil (P=0.012). In the physicians' evaluations, there was a significant and comparable reduction in erythema, conjunctival injection and overall conjunctival signs with both treatments from baseline. Improvement in edema and discharge were not significant with either drug. Quality of life scores (as measured by RQLQ) improved following treatment with nedocromil (P=0.0001) and olopatadine (P=0.0001). The improvement was comparable with the two drugs (P=0.603). Nedocromil and olopatadine were similarly effective in preventing onset of allergic signs and symptoms. Both physicians and patients rated nedocromil as moderately or completely effective in 18 patients and olopatadine as moderately or completely effective in 17 patients.
Owen et al.[52] (2004) Ophthalmic antihistamines (antazoline* one trial, azelastine one trial, emedastine one trial, levocabastine* six trials)	MA (40 DB, RCTs) Patients with seasonal allergic conjunctivitis	N=not reported Duration varied	Primary: Subjective symptoms (e.g., ocular itching, burning, soreness and lacrimation) and patient's perception of improvement in subjective symptoms	Primary: Most trials showed improvement in symptoms, especially for itching, in those treated with antihistamines compared to placebo. No antihistamine was more effective than another. Limited evidence suggests that antihistamines have a faster therapeutic effect compared to mast cell stabilizers; however, there was little difference in treatment efficacy after two weeks. Two short-term allergen provocation trials reported significantly less ocular itching and redness in patients treated with antihistamines compared to patients treated with mast cell stabilizers (P<0.05); however,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ophthalmic mast cell stabilizers (cromolyn 17 trials, lodoxamide one trial and nedocromil five trials) vs ophthalmic mast cell stabilizers (cromolyn five trials, lodoxamide one trial and nedocromil two trials) vs placebo			Secondary: Not reported	no significant differences in subjective symptoms were noted in six long-term studies. Patients using antihistamines were 1.3 times (95% CI, 0.8 to 2.2) more likely to perceive a "good" treatment effect compared to patients using mast cell stabilizers; however, this was not statistically significant. Eight studies recorded subjective symptoms comparing cromolyn to placebo. An improvement in subjective symptoms was reported in five studies with no difference between treatments reported in three trials. A MA of six trials demonstrated that patients using cromolyn were 17 times (95% CI, 4 to 78) more likely to perceive benefit than those using placebo (of note, trials reporting marked and statistically significant benefits of cromolyn over placebo had small sample sizes.) No clinically relevant adverse events were reported with cromolyn treatment. In a small trial lasting four weeks, patients using lodoxamide reported significantly fewer symptoms of burning and itching, eyelid swelling, lacrimation and photophobia compared to those using placebo (P values not reported). Subjective symptoms were less pronounced in patients using nedocromil compared to patients using placebo with the differences reported as statistically significant in three studies. Patients using nedocromil were 1.8 times (95% CI, 1.3 to 2.6) more likely to report that their symptoms were "moderately" or "totally" controlled than those receiving placebo. Unpleasant taste following administration was the most reported adverse event. Patients using mast cell stabilizers were 4.9 times (95% CI, 2.5 to 9.6) more likely to perceive benefit from treatment compared to patients receiving placebo. No trials directly compared mast cell stabilizers with one another. Secondary: Not reported
Allergic Rhinitis				
Stern et al.[53]	DB, MC, PC, PG,	N=195	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Azelastine nasal spray vs budesonide nasal spray	RCT Patients with perennial allergic rhinitis	6 weeks	Daily nasal symptom scores (combined nasal symptoms, blocked nose, rhinorrhea, sneezing), patients' overall assessment of treatment efficacy, use of terfenadine tablets as rescue medication Secondary: Not reported	The reduction in all individual nasal symptoms from baseline was greater with the budesonide group compared to those treated with azelastine (P≤0.05). Azelastine did not produce a significant improvement in either combined or individual nasal symptoms (P>0.05). The patients' overall assessments of treatment efficacy after six weeks of therapy showed that budesonide was significantly more effective compared to both azelastine and placebo (P=0.013 and P=0.0003 respectively). There was no significant difference between azelastine and placebo with respect to the degree of symptom control achieved (P=0.20). The reduction in the use of terfenadine from baseline was significantly greater for budesonide (P=0.0033) and azelastine (P=0.0015) compared to placebo, but there was no difference between the two active treatments (P=0.80). Secondary: Not reported
Corren et al.[54] (2005) Azelastine nasal spray vs cetirizine 10 mg tablets	DB, MC, PG, RCT Patients with moderate to severe seasonal allergic rhinitis	N=229 2 weeks	Primary: Change from baseline to day 12 in the 12-hour reflective TNSS, including rhinorrhea, sneezing, itchy nose, nasal congestion Secondary: Not reported	Primary: Both groups had significant improvements in the TNSS compared to baseline (P<0.001). The overall TNSS was significantly greater with azelastine nasal spray compared to cetirizine (P=0.015). Azelastine nasal spray significantly improved the instantaneous TNSS compared to cetirizine at 60 and 240 minutes after the initial dose (P=0.040). Secondary: Not reported
Shah et al.[55] (2009) Olopatadine 0.6% 2 sprays in each nostril BID	AC, DB, MC, PC, PG, RCT Patients ≥12 years of age with a history of seasonal allergic	N=544 16 days	Primary: TNSS, quality of life (RQLQ), tolerability Secondary:	Primary: The mean change from baseline in overall TNSS was significantly greater with olopatadine (26.8%) compared to placebo (18.4%; P=0.003). The mean change from baseline in overall TNSS was 29.9% with azelastine. The difference between active treatments was nonsignificant (95% CI, -2.5 to 8.7).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs azelastine 0.1% 2 sprays in each nostril BID vs placebo	rhinitis		Not reported	The mean change in overall RQLQ score was significantly greater with olopatadine compared to placebo (P=0.005). There was no significant difference between active treatments. The most commonly reported adverse event in the olopatadine and azelastine groups was bitter taste (12.2 and 19.7%, respectively). In the placebo group, bitter taste (1.7%) and nasal discomfort (1.7%) were the most frequently reported adverse events. The prevalence of bitter taste was significantly lower in the olopatadine treatment group compared to the azelastine group (P=0.05). Among patients who reported bitter taste, the proportion who rated the event as severe was significantly lower in the olopatadine group compared to the azelastine group (0 vs 8.1%; P=0.005). The majority of bitter taste events reported in the olopatadine group were mild (72.7%), whereas the majority of these events in the azelastine group were reported as moderate (56.8%). Secondary: Not reported
Meltzer et al.[56] (2008) Olopatadine 0.6% 2 sprays in each nostril vs azelastine 0.1% 2 sprays in each nostril	DB, MC, RCT, XO Patients ≥18 years of age with a ≥2 year history of allergic rhinitis (seasonal or perennial) who were symptomatic at the time of enrollment	N=110 Single dose	Primary: Patient preference based on overall aftertaste of each medication Secondary: Not reported	Primary: Overall, 60.6% of the patients favored olopatadine, 30.3% favored azelastine, and 9.2% indicated no preference. Olopatadine was more effective than azelastine in patient perceptions of aftertaste (P<0.0005). For overall patient preference, olopatadine was more effective than azelastine at visit 4 was (P=0.0001). The mean response for likelihood of use (0.8 U) indicated a preference for olopatadine over azelastine (P=0.0004). Overall, 62.4 and 60.9% of patients favored olopatadine in regards to patient preference and likelihood of use, respectively. Olopatadine was shown to be statistically superior to azelastine in patient perceptions of taste immediately after study drug administration (P<0.0001). Immediately after dosing, patients reported a significant difference in favor of olopatadine relative to azelastine with regard to several attributes: the smell of the medication (P=0.0002); nasal irritation (P<0.0001); urge to sneeze (P=0.0146); dripping out of the nose (P=0.0008); dripping down

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the throat (P=0.0004); and overall satisfaction (P<0.0001). No significant difference was observed for moistness of the nose or throat (P=0.1723). When assessed at 45 minutes post-dosing, a difference in favor of olopatadine relative to azelastine was observed for nasal irritation (P=0.0048), urge to sneeze (P=0.0174), and overall satisfaction (P=0.0487). No significant differences were observed for the remaining variables at this time point (P≥0.0933 for each of the remaining variables). At visit 4, after having received both treatments, patients indicated a favorable preference for olopatadine in all of the assessed variables (P≤0.0036 for each variable). Secondary: Not reported
Multiple Ocular Infections				
Kjellman et al.[57] (1995) Nedocromil 2% BID or QID vs placebo Additional information was not provided.	MA (26 trials) Patients 3 to 76 years of age with seasonal allergic conjunctivitis, perennial allergic conjunctivitis, and vernal kerato-conjunctivitis	N=2,905 Duration varied	Primary: Efficacy, safety Secondary: Not reported	Primary: In the treatment of vernal keratoconjunctivitis, nedocromil QID was significantly more effective than placebo (P value not reported). Clinicians reported good control in 76 and 46% of patients receiving nedocromil and placebo, respectively (P<0.001). Nedocromil when dosed either BID or QID was statistically better than placebo for the treatment of seasonal allergic conjunctivitis (P value not reported). The speed of action was assessed in seven trials with 50 and 74% of patients experiencing relief of symptoms within 15 and 60 minutes after dosing, respectively. Patients with chronic symptoms of perennial allergic conjunctivitis responded better to nedocromil QID compared to BID, and significantly more patients were effectively controlled by nedocromil QID (72%) compared to placebo (47%; P value not reported). Nedocromil was well accepted in both adults and children with no major adverse events reported. Minor irritations, burning, or stinging of the eyes and a distinctive taste were reported more frequently with nedocromil than placebo (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Vernal Keratoconjunctivitis				
Foster.[58] (1998) Cromolyn 4% both eyes vs placebo Additional information was not reported.	DB, MC, PC, RCT Patients with bilateral vernal kerato-conjunctivitis (age not reported)	N=65 6 weeks	Primary: Signs and symptoms, symptoms summary score Secondary: Not reported	Primary: Cromolyn was found to be significantly more effective than placebo in treating the signs and symptoms of vernal keratoconjunctivitis, such as conjunctival injection, limbal injection, limbal edema, tearing, and symptoms summary score (P values not reported). There were few side effects (primarily mild stinging and burning, which did not require drug discontinuation). Secondary: Not reported
Leonardi et al.[59] (1997) Cromolyn 4% both eyes QID vs lodoxamide 0.1% both eyes QID	DB, RCT Patients with mild to moderate vernal kerato-conjunctivitis, mean age 12 years	N=30 10 days	Primary: Clinical score for major signs and symptoms of vernal kerato-conjunctivitis Secondary: Not reported	Primary: The mean clinical score for signs and symptoms of vernal keratoconjunctivitis did not improve significantly from baseline in patients treated with cromolyn but improved significantly in patients treated with lodoxamide (P<0.001). The mean clinical score was unchanged in 42 and 15% of the cromolyn and lodoxamide treated eyes, respectively. Lodoxamide was significantly more effective than cromolyn (P<0.005) in reducing chemosis, discharge, foreign body sensation, hyperemia, itching, photophobia, tearing, and corneal epitheliopathy; but not limbal infiltrates and papillae. Secondary: Not reported
Caldwell et al.[60] (1992) Cromolyn 4% QID vs lodoxamide 0.1%	DB, MC, PG Patients with vernal kerato-conjunctivitis	N=120 28 days	Primary: Signs and symptoms Secondary: Not reported	Primary: On various follow-up visits, the clinical efficacy of lodoxamide was statistically "superior" to cromolyn in alleviating five of the major signs (Trantas' dots, palpebral conjunctival changes, bulbar conjunctival hyperemia, erythema/swelling of eyelids and periorbital tissues, and epithelial disease) and four of the primary symptoms (discomfort, foreign body sensation, itching, and tearing) of vernal keratoconjunctivitis (P values not reported). At no time during the study was cromolyn

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QID Additional information was not reported.				statistically "superior" to lodoxamide in demonstrating improvements in clinical signs and symptoms of vernal keratoconjunctivitis. The physician's clinical judgment of patients' response to treatment showed lodoxamide produced a greater and earlier improvement than cromolyn. Both drugs were safe for topical ophthalmic use when used QID for up to 28 days. Secondary: Not reported
Avunduk et al.[61] (2000) Cromolyn 4% 2 drops both eyes QID vs lodoxamide 0.1% 2 drops both eyes QID	DB, RCT Patients with vernal kerato-conjunctivitis, mean age 13 years	N=30 Duration not reported	Primary: Eye symptom severity scores Secondary: Not reported	Primary: Patient symptom scores and clinical signs were significantly lower after treatment with either cromolyn or lodoxamide compared to pretreatment values (P<0.025). Patients treated with lodoxamide had significantly lower symptom scores and clinical signs than patients treated with cromolyn (P<0.025). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily
Study Design abbreviations: AC=active controlled, DB=double blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single blind, XO=cross over
Miscellaneous abbreviations: CAC=conjunctival allergen challenge, CI=confidence interval, MAR=minimum angle of resolution, NOCS=non-ocular composite symptom, OPI=Ocular Protection Index, RQLQ=Rhinoconjunctivitis *Quality of Life* Questionnaire, TNSS=total nasal symptom score

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 8. Relative Cost of the Eye, Ear, Nose, and Throat (EENT) Antiallergic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azelastine	solution*†‡	N/A	N/A	$
Bepotastine	solution*	Bepreve®	$$$$$	$$$$$
Cetirizine	solution*	N/A	N/A	$
Cromolyn	solution*‡	N/A	N/A	$$$
Epinastine	solution*‡	N/A	N/A	$
Lodoxamide	solution*	Alomide®	$$$$$	N/A
Nedocromil	solution*	Alocril®	$$$$$	N/A
Olopatadine	solution*†‡	Pataday®*‡, Patanase®†‡, Patanol®*‡, Pazeo®*	$$$$$	$

*Ophthalmic formulation.
†Nasal formulation.
‡Generic is available in at least one dosage form and/or strength.
N/A=not available.

X. Conclusions

The eye, ear, nose, and throat (EENT) antiallergic agents are approved for the treatment of allergic conjunctivitis and rhinitis. They are available in both nasal and ophthalmic formulations.[1-12] Cetirizine is a histamine H_1-receptor antagonist. Cromolyn, lodoxamide, and nedocromil are mast cell stabilizers. Azelastine, bepotastine, epinastine,

and olopatadine are antihistamines with mast cell stabilizing properties.[1,2] Azelastine, cromolyn, epinastine, and olopatadine are available in a generic formulation.

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists, and mast cell stabilizers. Many of these agents can also benefit associated symptoms of allergic conjunctivitis. The selection of therapy should be individualized and take into consideration the severity and duration of the disease, patient preference, efficacy, and safety. In general, guidelines do not give preference to one EENT antiallergic agent over another. Ophthalmic products may be preferred to oral formulations if ocular symptoms are the primary manifestation of the disease as they are faster-acting and are less likely to cause systemic adverse events. The dual action antiallergic agents treat signs and symptoms of allergic conjunctivitis during the acute phase (antihistaminic action) and prevent mast cell degranulation (membrane stabilizing action). Thus, they are suitable for both the acute and long-term management of allergic conjunctivitis. The onset of action for mast cell stabilizers is five to fourteen days; therefore, they are not useful for treating acute symptoms.[13-20]

There are relatively few comparative studies that have been conducted with the EENT antiallergic agents in a 'real-life' setting. While some of these trials have demonstrated similar outcomes with regards to ocular symptoms, nasal symptoms, and patient preference, other studies have demonstrated greater efficacy with one agent over another.[21,26,34,37,41,42,45,47-49,51,55,56,59-61] Many comparative studies have been performed using environmental challenge chambers. However, the antiallergic agents are typically administered as a single dose and the clinical outcomes are assessed after several minutes or hours.[28,31-33,35,36,39,40,43,44,46,50]

There is insufficient evidence to support that one brand EENT antiallergic agent is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT antiallergic agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (EENT) antiallergic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Antibacterials
AHFS Class 520404
August 10, 2022

I. Overview

The eye, ear, nose, and throat (EENT) antibacterials are used to treat a variety of infections. The agents in this class are administered topically and include aminoglycosides, macrolides, quinolones, sulfonamides, as well as several miscellaneous antibacterials.[1-26] The products are available as single entity formulations, as well as in combination with other antibacterial agents or corticosteroids. Oral doxycycline (subantimicrobial dose formulation) is also included in this review as it is approved for the treatment of periodontal disease.[1,26]

The ophthalmic antibacterials are used to treat infections of the eye, including blepharitis, conjunctivitis, keratitis, as well as others. Bacterial overgrowth plays a role in the pathophysiology of blepharitis, and *Staphylococcus* species, *Corynebacterium* species, and *Propionibacterium acnes* are the most common pathogens.[27] Patient education on self-care hygiene is an essential component of treatment and topical antibacterials are frequently used to reduce bacterial load.[27,28] Bacterial conjunctivitis is highly contagious and symptoms include redness of the eye and thick, purulent discharge.[29,30] Common pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis,* and *Haemophilus influenzae*.[30] Bacterial conjunctivitis is a self-limiting condition; however, the use of topical antibacterials may shorten the clinical course and reduce transmission to others.[29,30] Soft contact lens wearers with conjunctivitis have a high incidence of infection with *Pseudomonas* and quinolones are the preferred treatment option in this patient population. Antibacterials containing corticosteroids are generally not appropriate for the acute treatment of bacterial conjunctivitis.[30] Corneal abrasions may occur spontaneously or may be due to trauma, the presence of a foreign body, or contact lenses. The prophylactic use of topical antibacterials is often employed to prevent superinfections.[31] Keratitis is an inflammatory condition affecting the cornea and is associated with moderate to intense pain.[32] Common pathogens include *Staphylococcus* species, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae,* and polymicrobial isolates. Corneal scarring and loss of vision may occur very quickly; therefore, patients should be evaluated by an ophthalmologist on the same day and receive prompt treatment with a topical antibacterial agent.[32,33] Bacterial endophthalmitis is a vision-threatening bacterial infection of the aqueous or vitreous humor of the eye, which may occur following intraocular surgery or perforating trauma.[32,34] Staphylococci are the major pathogens in endophthalmitis. Treatment is emergent and may include direct injection of antibiotics into the vitreous humor or systemic administration. The role of topical antibacterials in the treatment of endophthalmitis is less clear.[34]

The otic antibacterials are approved for the treatment of otitis externa and otitis media. Otitis externa is an inflammatory condition of the external ear canal which may be classified as infectious or non-infectious. Common infectious pathogens include *Staphylococcus aureus* and *Pseudomonas aeruginosa*; however, polymicrobic infections occur frequently.[35,36] Topical antibacterials (alone or in combination with a corticosteroid) are very effective and systemic therapy is generally not required.[35,37] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss, and vertigo. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis*.[38,39] Oral antibacterials are generally the initial treatment option; however, topical antibacterials may be used in patients with perforated tympanic membranes, tympanostomy tubes, or chronic suppurative otitis media.[39,40]

Periodontitis is an inflammatory condition of the periodontium, which is due to the presence of bacterial plaque on adjacent teeth.[41] Treatment includes scaling and root planing, as well as adjunctive therapy with an antimicrobial agent to reduce the bacterial load. Doxycycline has been shown to reduce collagenase activity in gingival tissues and fluid, and may prevent further breakdown of connective tissue and alveolar bone.[1,26,42] The dose of doxycycline used for the treatment of periodontitis (20 mg twice daily) differs from that used to treat infections. This subantimicrobial dose is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis.[1,26]

The EENT antibacterials that are included in this review are listed in Table 1. This review encompasses all EENT antibacterial dosage forms and strengths. The topical antibacterials (AHFS 840404) and systemic antibacterials (AHFS 081200) were previously reviewed and are not included in this review. Many of the products are available in a generic formulation. This class was last reviewed in May 2020.

Table 1. EENT Antibacterials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Azithromycin	solution*	AzaSite®	none
Bacitracin	ointment*	N/A	bacitracin
Besifloxacin	suspension*	Besivance®	Besivance®
Ciprofloxacin	ointment*, solution*§‡, suspension†	Ciloxan®§	ciprofloxacin
Doxycycline	tablet§	N/A	doxycycline
Erythromycin base	ointment*	N/A	erythromycin base
Gatifloxacin	solution*	Zymaxid®§	gatifloxacin
Gentamicin	ointment*, solution*	N/A	gentamicin
Levofloxacin	solution*	N/A	levofloxacin
Moxifloxacin	solution*	Vigamox®§	moxifloxacin
Ofloxacin	solution*†	Ocuflox®§	ofloxacin
Sulfacetamide	ointment*, solution*	N/A	sulfacetamide
Tobramycin	ointment*, solution*	Tobrex®§ ointment	tobramycin
Combination Products			
Bacitracin and polymyxin B	ointment*	N/A	bacitracin and polymyxin B
Ciprofloxacin and dexamethasone	suspension†*	Ciprodex®§	Ciprodex®
Ciprofloxacin and fluocinolone	solution†*	Otovel®§	ciprofloxacin and fluocinolone
Ciprofloxacin and hydrocortisone	suspension†	Cipro HC®	Cipro HC®
Gentamicin and prednisolone	ointment*, suspension*	Pred-G® ointment	none
Neomycin, bacitracin, and polymyxin B	ointment*	N/A	neomycin, bacitracin and polymyxin B
Neomycin, bacitracin, polymyxin B and hydrocortisone	ointment*	N/A	neomycin, bacitracin, polymyxin B and hydrocortisone
Neomycin, colistin, hydrocortisone and thonzonium	suspension†	Cortisporin-TC®	none
Neomycin, polymyxin B and dexamethasone	ointment*, suspension*	Maxitrol®§	neomycin, polymyxin B and dexamethasone
Neomycin, polymyxin B and gramicidin	solution*	N/A	neomycin, polymyxin B and gramicidin
Neomycin, polymyxin B and hydrocortisone	solution†, suspension*†	N/A	neomycin, polymyxin B and hydrocortisone
Polymyxin B and trimethoprim	solution*	Polytrim®§	polymyxin B and trimethoprim
Sulfacetamide and prednisolone	ointment*, solution*§, suspension*	Blephamide® ointment	sulfacetamide and prednisolone, Blephamide® ointment
Tobramycin and dexamethasone	ointment*, suspension*	TobraDex®§, TobraDex ST®	tobramycin and dexamethasone
Tobramycin and loteprednol	suspension*	Zylet®	Zylet®

*Ophthalmic formulation.
†Otic formulation.
§Generic is available in at least one dosage form and/or strength.

N/A=Not available, PDL=Preferred Drug List

The EENT antibacterials have been shown to be active against the strains of microorganisms indicated in Tables 2 and 3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the EENT antibacterials that are noted in Tables 5 and 6.

Table 2. Microorganisms Susceptible to the EENT Antibacterials-Single Entity Agents[1-26]

Organism	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Gram-Positive Aerobes													
Bacillus anthracis					✔								
CDC coryneform group g	✔		✔										
Corynebacterium propinquum							✔						
Corynebacterium pseudodiphtheriticum			✔										
Corynebacterium striatum			✔										
Corynebacterium species		✔				✔			✔	✔			
Listeria monocytogenes					✔								
Micrococcus luteus										✔			
Staphylococcus aureus	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔
Staphylococcus aureus (methicillin-resistant)													
Staphylococcus epidermidis			✔	✔			✔	✔	✔	✔	✔		✔
Staphylococcus haemolyticus										✔			
Staphylococcus hominis			✔							✔			
Staphylococcus lugdunensis			✔										
Staphylococcus species		✔											
Staphylococcus warneri										✔			
Streptococcus mitis group	✔		✔				✔						
Streptococcus oralis			✔				✔						
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Streptococcus pyogenes		✔				✔		✔					
Streptococcus salivarius			✔										
Streptococcus species		✔											✔
Streptococcus (Groups C/F)									✔				
Streptococcus (Group G)									✔				
Streptococcus (Viridans Group)				✔		✔			✔	✔		✔	
Gram-Negative Aerobes													
Acinetobacter calcoaceticus													✔
Acinetobacter lwoffi									✔	✔			
Acinetobacter species					✔								
Bartonella bacilliformis					✔								
Brucella species					✔								
Campylobacter fetus					✔								
Chlamydia trachomatis					✔	✔				✔			
Enterobacter aerogenes					✔			✔					✔
Enterobacter cloacae											✔		
Enterobacter species												✔	
Escherichia coli					✔			✔			✔	✔	✔
Francisella tularensis					✔								
Haemophilus aegyptius													✔
Haemophilus ducreyi					✔								
Haemophilus influenzae	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Organism	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Haemophilus parainfluenzae										✔			
Klebsiella granulomatis					✔								
Klebsiella pneumoniae								✔				✔	✔
Klebsiella species					✔								
Moraxella catarrhalis											✔		
Moraxella lacunata			✔										✔
Morganella morganii													✔
Neisseria gonorrhea		✔			✔	✔		✔					
Neisseria species		✔											✔
Proteus mirabilis											✔		✔
Proteus vulgaris													✔
Pseudomonas aeruginosa				✔				✔	✔		✔		
Serratia marcescens				✔				✔	✔		✔		
Shigella species					✔								
Vibrio cholerae					✔								
Yersinia pestis					✔								
Anaerobic Species													
Clostridium species					✔								
Fusobacterium fusiforme					✔								
Propionibacterium acnes					✔						✔		

Table 3. Microorganisms Susceptible to the EENT Antibacterials-Combination Products[1-26]

Organism	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimet-hoprim	Sulface-tamide and PRED	TOBY and DEX	TOBY and Lotep-rednol
Gram-Positive Aerobes															
Corynebacterium species	✔														
Staphylococcus aureus	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Staphylococcus epidermidis														✔	✔
Staphylococcus species	✔														
Streptococcus pneumoniae	✔	✔	✔		✔	✔	✔			✔		✔	✔	✔	✔
Streptococcus pyogenes	✔				✔										
Streptococcus species	✔													✔	✔

Organism	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocinolone	CIPRO and HYDRO	Gentamicin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimethoprim	Sulfacetamide and PRED	TOBY and DEX	TOBY and Loteprednol
Streptococcus (Viridans Group)													✔		
Gram-Negative Aerobes															
Acinetobacter calcoaceticus														✔	✔
Enterobacter aerogenes	✔				✔							✔		✔	✔
Enterobacter species						✔	✔	✔	✔	✔	✔		✔		
Escherichia coli	✔				✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Haemophilus aegyptius														✔	✔
Haemophilus influenzae	✔	✔	✔		✔	✔	✔		✔	✔	✔	✔	✔	✔	✔
Haemophilus parainfluenzae															
Klebsiella pneumoniae	✔				✔	✔	✔	✔				✔	✔	✔	✔
Klebsiella species									✔	✔	✔				
Moraxella catarrhalis		✔	✔												
Moraxella lacunata														✔	✔
Morganella morganii														✔	✔
Neisseria gonorrhoeae	✔				✔										
Neisseria species	✔					✔	✔		✔	✔	✔			✔	✔
Proteus mirabilis				✔										✔	✔
Proteus species												✔			
Proteus vulgaris														✔	✔
Pseudomonas aeruginosa	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔
Serratia marcescens					✔										

BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) antibacterials are summarized in Table 4.

Table 4. Treatment Guidelines Using the EENT Antibacterials

Clinical Guideline	Recommendations

American Academy of Ophthalmology: **Preferred Practice Pattern: Blepharitis (2018)**[27]	• The patient must understand that a cure is usually not possible.
	• Treatments that are helpful include the following:
	  o Warm compresses.
	  o Eyelid cleansing, including eyelid massage in cases of meibomian gland dysfunction (MGD) to express the meibomian glands.
	  o Antibiotics (topical and/or systemic).
	  o Ophthalmic anti-inflammatory agents (e.g., corticosteroids, cyclosporine).
	• These treatment options are often used in combination.
	• Eyelid cleansing is especially useful for anterior blepharitis, and warm compresses are especially helpful for posterior blepharitis and MGD.
	• Optimal treatment regimens often require a trial and error approach.
	• Topical antibiotics have been shown to provide some symptomatic relief, and they have been effective in decreasing bacteria from the eyelid margin in cases of anterior blepharitis.
	• Evidence on the effectiveness of some treatments for blepharitis, such as topical corticosteroids or oral antibiotics, has been shown to be inconclusive.
	• A topical antibiotic ointment such as bacitracin or erythromycin can be prescribed and applied on the eyelid margins one or more times daily or at bedtime for a few weeks. Topical antibiotic treatment can be repeated on an intermittent basis using different kinds of medications with different mechanisms of action to prevent the development of resistant organisms.
	• The combination of tobramycin/dexamethasone ophthalmic suspension and azithromycin in a sustained-release system has been evaluated and appears to reduce some of the symptoms of blepharitis, but its use for this indication has not been approved by the FDA.
	• For patients with MGD, whose chronic signs and symptoms are not adequately controlled with eyelid hygiene or meibomian gland expression, an oral tetracycline and topical antibiotics can be prescribed.
	• Doxycycline, minocycline, or tetracycline can be given daily, and tapered after clinical improvement is noted. Alternatively, oral erythromycin or azithromycin can be used especially in women of childbearing age and children.
	• Tetracyclines and macrolide antibiotics also have anti-inflammatory activity.
	• Treatments can be intermittently discontinued and reinstated, based on the severity of the patient's blepharitis and tolerance for the medication.
	• A brief course of topical corticosteroids may be helpful for eyelid or ocular surface inflammation such as severe conjunctival infection, marginal keratitis, or phlyctenules. Ophthalmic corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface.
	• Once the inflammation is controlled, the ophthalmic corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort.
	• The minimal effective dose of ophthalmic corticosteroid should be utilized, and long-term ophthalmic corticosteroid therapy should be avoided if possible.
	• Potential adverse effects of ophthalmic corticosteroid use, including the risk for developing increased intraocular pressure and cataracts may be minimized by using a site-specific ophthalmic corticosteroid such as ophthalmic loteprednol etabonate and ophthalmic corticosteroids with limited ocular penetration, such as ophthalmic fluorometholone.
	• Topical cyclosporine may be helpful in some patients with posterior blepharitis.
	• Artificial tears may improve symptoms when used as an adjunct to eyelid hygiene

Clinical Guideline	Recommendations
	and medications. If used more than four times per day, non-preserved tears should be used to avoid preservative toxicity.
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2018)**[29]	Seasonal allergic conjunctivitis • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • The use of topical mast-cell inhibitors can also be helpful in alleviating the symptoms of allergic rhinitis. Mast-cell inhibitors formulated as a nasal spray and aerosols are also helpful in alleviating the symptoms of allergic rhinitis and asthma in some patients. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a topical corticosteroid with a low side effect profile can be added to the regimen. • Oral antihistamines are commonly used but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and actually worsen allergic conjunctivitis. • Concomitant use of cooled artificial tears may alleviate coexisting tear deficiency and dilute allergens and inflammatory mediators on the ocular surface. • In severe cases, topical cyclosporine or tacrolimus can be considered. Vernal/atopic conjunctivitis • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. Systemic immunosuppression is rarely warranted, but options include montelukast, aspirin, interferons, and oral T-cell inhibitors, such as cyclosporine and tacrolimus. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
College of Optometrists: **Clinical Management Guideline on Bacterial Conjunctivitis (2021)**[43]	Etiology • Self-limiting bacterial infection of the conjunctiva, typically by: o *Staphylococcus* species o *Streptococcus pneumoniae* o *Haemophilus influenzae* o *Moraxella catarrhalis* Predisposing factors • Children and the elderly have an increased risk of infective conjunctivitis o contamination of the conjunctival surface o superficial trauma o contact lens wear (infection may be Gram-negative) o secondary to viral conjunctivitis o diabetes (or other disease compromising the immune system) o steroids (systemic or topical, compromising ocular resistance to infection) o blepharitis (or other chronic ocular inflammation)

Clinical Guideline	Recommendations
	Symptoms • Acute onset of: o redness o discomfort, usually described as burning or grittiness o discharge (may cause temporary blurring of vision) o crusting of lids (often stuck together after sleep and may have to be bathed open) • Usually bilateral – one eye may be affected before the other (by one or two days) Management by optometrist • Practitioners should recognize their limitations and where necessary seek further advice or refer the patient elsewhere • Non pharmacological o Often resolves in five to seven days without treatment o Bathe/clean the eyelids with proprietary sterile wipes, lint or cotton wool dipped in sterile saline or boiled (cooled) water to remove crusting o Advise patient that condition is contagious (do not share towels, etc.) • Pharmacological o Treatment with topical antibiotic may improve short-term outcome and render patient less infectious to others o Topical antibiotics (with no evidence of superiority of particular antibiotics) may include: chloramphenicol 0.5% eye drops, chloramphenicol 1% ointment, azithromycin 1.5% eye drops, fusidic acid 1% viscous eye drops (note high cost and narrower spectrum of activity than chloramphenicol) o Predictors of bacterial culture positivity at presentation include purulent discharge and age less than five years o Contact lens wearers with a diagnosis of bacterial conjunctivitis should be treated with a topical antibiotic effective against Gram-negative organisms, e.g. a quinolone such as levofloxacin or moxifloxacin, or an aminoglycoside such as gentamicin. Contact lenses should not be worn during the treatment period o Advise patient to return/seek further help if symptoms persist beyond seven days Possible management by ophthalmologist • If resistant to treatment, or recurrent: o conjunctival swabs taken for microscopy and culture and/or polymerase chain reaction analysis • treatment with other antibiotics, based on culture results
American Academy of Ophthalmology: **Preferred Practice Pattern: Bacterial Keratitis (2018)**[33]	Initial treatment • Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. • Ophthalmic ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. • The recommended ophthalmic empiric treatments include: o No organism identified or multiple types of organisms: ophthalmic cefazolin or vancomycin with tobramycin or gentamicin or fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin, and moxifloxacin, and besifloxacin than other fluoroquinolones). o Gram-positive cocci: ophthalmic cefazolin, vancomycin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), ophthalmic bacitracin (for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy), or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin, and moxifloxacin, and besifloxacin than other fluoroquinolones).

Clinical Guideline	Recommendations
	○ Gram-negative rods: ophthalmic formulations of tobramycin or gentamicin, ceftazidime, or fluoroquinolones. ○ Gram-negative cocci: ophthalmic ceftazidime, ceftriaxone, or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection). ○ Gram-positive rods (Nontuberculous mycobacteria): ophthalmic amikacin, azithromycin, clarithromycin, or fluoroquinolones. ○ Gram-positive rods (Nocardia): ophthalmic amikacin, sulfacetamide, or trimethoprim/sulfamethoxazole. • Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. Ciprofloxacin 0.3%, ofloxacin 0.3% and levofloxacin 1.5% are FDA-approved for this indication. The fourth generation fluoroquinolones (gatifloxacin and moxifloxacin) have not been approved for the treatment of bacteria keratitis; however, both agents have performed at least as well as standard therapy, fortified cefazolin/tobramycin combination therapy and potentially better than ciprofloxacin. • Some pathogens (e.g., *Streptococci*, anaerobes) reportedly have variable susceptibility to ophthalmic fluoroquinolones, and the prevalence of resistance to fluoroquinolones appears to be increasing. • Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment. • Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with laser in situ keratomileusis. • Methicillin-resistant and oxacillin-resistant *S. aureus* has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Ophthalmic fluoroquinolones are generally poorly effective against MRSA ocular isolates. MRSA isolates are generally sensitive to ophthalmic vancomycin. • Systemic antibiotics are rarely needed, but they may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. • Systemic therapy is necessary in cases of gonococcal keratitis. <u>Corticosteroid therapy</u> • Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. • Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting and increased intraocular pressure. • There is no conclusive evidence that ophthalmic corticosteroids alter clinical outcome. • Despite risks involved, it is believed that sensible use of ophthalmic corticosteroids can reduce morbidity. • Patients being treated with ophthalmic corticosteroids at the time of presentation of suspected bacterial keratitis should have their ophthalmic corticosteroid regimen reduced or eliminated until the infection has been controlled. • Inflammation and symptoms may temporarily increase as ophthalmic corticosteroids are reduced because of the lack of local immune suppression. • The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation.

Clinical Guideline	Recommendations
	Modification of therapy • Efficacy of the regimen is judged primarily by clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. • When the patient is improving, therapy need not be adjusted solely on the basis of laboratory studies. • Dual antibiotic treatment designed to achieve broad-spectrum coverage may become unnecessary once the causative organism has been isolated. • The initial therapeutic regimen should be modified (change in type, concentration or frequency of antibiotic) when the eye shows a lack of improvement or stabilization within 48 hours. • Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are sub-therapeutic and may increase the risk of developing antibiotic resistance.
American Optometric Association: **Care of the Patient with Ocular Surface Disorders (2010)**[44]	Blepharitis • Lid hygiene is essential but alone will not resolve blepharitis. • Appropriate anti-infective drugs can be administered topically, systemically, or in combination. • Aggressive therapy should initially include a minimum of six weeks of lid hygiene and appropriate anti-infective medications to gain control of the condition, followed by maintenance therapy. • For patients without lid margin disease, the initial treatment consists of topical tear supplements and immunomodulators. Failure to respond should prompt pursuit of signs of posterior blepharitis. Staphylococcal blepharitis • Treatment includes an antibiotic ointment to control the infection, as well as lid hygiene. • Erythromycin, bacitracin, polymyxin B and bacitracin combination, gentamicin, and tobramycin are all effective antibiotics for treatment of staphylococcal blepharitis. • Antibiotic eye drops can be used, but they do not work as well as ointments due to reduced contact time. • Tear supplements may also be required to alleviate symptoms. • If peripheral corneal infiltrates are present without epithelial defects, topical steroids may be used for a limited time.
American Academy of Otolaryngology-Head and Neck Surgery Foundation: **Clinical Practice Guideline: Acute Otitis Externa (Update) (2014)**[35]	• Other causes of otalgia, otorrhea, and inflammation of the external ear canal should be distinguished when diagnosing patients with diffuse acute otitis externa (AOE). • Patients with diffuse AOE should be assessed for factors that modify management strategies such as nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, and prior radiotherapy. • A diagnosis of diffuse AOE requires rapid onset of symptoms with signs of ear canal inflammation. Other symptoms include otalgia, itching, or fullness, with or without hearing loss or ear canal pain on chewing. In addition, tenderness of the tragus (when pushed), pinna (when pulled up and back), or both is a hallmark sign of diffuse AOE. • The management of diffuse AOE should include an assessment of pain with the clinician recommending analgesic treatment based on severity. • Clinicians should use topical preparations for initial therapy of diffuse, uncomplicated AOE. If the infection extends outside of the ear canal or there is presence of specific host factors that would indicate for systemic therapy, systemic antimicrobial therapy should be administered. • Topical preparations are recommended as initial therapy because of safety and efficacy over placebo in randomized controlled trials, and excellent clinical and

Clinical Guideline	Recommendations
	bacteriologic outcomes in comparative studies. • The choice of topical antimicrobial agent should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost. • Most of the currently available agents provide antimicrobial activity through an antibiotic, which may be an aminoglycoside, polymyxin B, a quinolone, or a combination of these agents; a steroid, such as dexamethasone or hydrocortisone; or a low pH antiseptic, such as acetic acid or aluminum acetate. • No significant differences in clinical outcomes of AOE were found for use of antimicrobial vs an antiseptic, a quinolone antibiotic vs a nonquinolone antibiotic(s), or a steroid-antimicrobial agent vs an antimicrobial agent alone. • Due to the lack of differences in efficacy among most topical antimicrobial and steroid preparations, patient preference and clinician experience are important aspects when selecting therapy. In addition, cost, adherence to therapy, and adverse events must also be taken into consideration. • Clinicians should inform patients of the proper way to administer topical drops. When the ear canal is obstructed, delivery of topical preparations should be enhanced by aural toilet, placement of a wick, or both. • When the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube, the clinician should prescribe a non-ototoxic topical preparation. • Patients who fail to respond to initial therapy within 48 to 72 hours should be reassessed to confirm the diagnosis of AOE and to exclude other causes of illness.
American Academy of Otolaryngology–Head and Neck Surgery, American Academy of Pediatrics, American Academy of Family Physicians: **Clinical Practice Guideline: Otitis Media with Effusion (Update) (2016)**[44]	• Clinicians should document the presence of middle ear effusion with pneumatic otoscopy when diagnosing otitis media with effusion (OME) in a child. • The clinician should perform pneumatic otoscopy to assess for OME in a child with otalgia, hearing loss, or both. • Obtain tympanometry in children with suspected OME for whom the diagnosis is uncertain after performing (or attempting) pneumatic otoscopy. • Educate families of children with OME regarding the natural history of OME, need for follow-up, and the possible sequelae. • Manage children with OME who are not at risk with watchful waiting for three months from the date of effusion onset (if known) or three months from the date of diagnosis (if onset is unknown). • Using intranasal or systemic steroids for treating OME is *not* recommended. • Using systemic antibiotics for treating OME is *not* recommended. • Using antihistamines, decongestants, or both for treating OME is *not* recommended. • Clinicians should re-evaluate, at three to six month intervals, children with chronic OME until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.
American Academy of Pediatrics: **Diagnosis and Management of Acute Otitis Media (2013)**[38]	• Clinicians should diagnose acute otitis media (AOM) in children who present with moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa. • Clinicians should diagnose AOM in children who present with mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM. • The management of AOM should include an assessment of pain. The management of pain, especially during the first 24 hours of an episode of AOM, should be addressed regardless of the use of antibiotics. • The clinician should prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (i.e., moderate or severe otalgia or otalgia for at least 48 hours, or temperature 102.2°F or higher). • The clinician should prescribe antibiotic therapy for bilateral AOM in children younger than 24 months without severe signs or symptoms (i.e., mild otalgia for less than 48 hours, temperature less than 102.2°F).

Clinical Guideline	Recommendations
	• The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for unilateral AOM in children 6 months of age and older without severe signs or symptoms. • High-dose amoxicillin is recommended as the first-line treatment in most patients, although there are a number of medications that are clinically effective. • Clinicians should prescribe amoxicillin for AOM when a decision to treat with antibiotics has been made and the child has not received amoxicillin in the past 30 days or the child does not have concurrent purulent conjunctivitis or the child is not allergic to penicillin. • Clinicians should prescribe an antibiotic with additional β-lactamase coverage for AOM when a decision to treat with antibiotics has been made and the child has received amoxicillin in the past 30 days or has concurrent purulent conjunctivitis or has a history of recurrent AOM unresponsive to amoxicillin. • Clinicians should reassess the patient if the caregiver reports that the child's symptoms have worsened or failed to respond to the initial antibiotic treatment within 48 to 72 hours and determine whether a change in therapy is needed. • In children with persistent, severe symptoms of AOM and unimproved otologic findings after initial treatment, the clinician may consider changing the antibiotic. If the child was initially treated with amoxicillin and failed to improve, amoxicillin-clavulanate should be used. Patients who were given amoxicillin-clavulanate or oral third-generation cephalosporins may receive intramuscular ceftriaxone (50 mg/kg). • In the treatment of AOM unresponsive to initial antibiotics, a 3-day course of ceftriaxone has been shown to be better than a 1-day regimen. • Clinicians should NOT prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the eye, ear, nose, and throat (EENT) antibacterials are noted in Tables 5 and 6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 5. FDA-Approved Indications for the EENT Antibacterials-Single Entity Agents[1-26]

Indication(s)	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gatif-loxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Ocular Disorders													
Acute bacterial meibomianitis								✔					
Bacterial blepharitis								✔					
Bacterial blepharoconjunctivitis								✔					
Bacterial conjunctivitis	✔		✔	✔		✔	✔	✔	✔	✔	✔	✔	
Bacterial corneal ulcers				✔ *		✔		✔			✔		
Bacterial dacryocystitis								✔					
Bacterial keratitis								✔					
Bacterial keratoconjunctivitis								✔					
Ocular infections due to susceptible microorganisms		✔										✔	✔
Prophylaxis of ophthalmia neonatorum due to *N gonorrhoeae* or *C trachomatis*						✔							
Otic Disorders													
Acute otitis media											✔		
Chronic suppurative otitis media											✔		
Otitis externa											✔		
The treatment of acute otitis externa due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*				✔									
Treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement				✔ †									
Miscellaneous Disorders													
Adjunct in systemic sulfonamide therapy of trachoma												✔ *	
Adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis					✔								

*Solution.
†Otic suspension.

Table 6. FDA-Approved Indications for the EENT Antibacterials-Combination Products[1-26]

Indication(s)	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocinolone	CIPRO and HYDRO	Gentamicin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimethoprim	Sulfacetamide and PRED	TOBY and DEX	TOBY and Loteprednol
Ocular Disorders															
Bacterial blepharitis						✔				✔					
Bacterial blepharoconjunctivitis						✔				✔		✔			
Bacterial conjunctivitis	✔					✔				✔		✔			
Bacterial corneal ulcers	✔														
Bacterial keratitis						✔				✔					
Bacterial keratoconjunctivitis						✔				✔					
Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists					✔		✔		✔		✔*		✔	✔	✔
Otic Disorders															
Acute otitis externa		✔		✔											
Acute otitis media															
Acute otitis media with tympanostomy tubes		✔	✔												
Bacterial infections of the external auditory canal								✔			✔				
Infections of mastoidectomy								✔			✔*				

Indication(s)	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trimet-hoprim	Sulfacet-amide and PRED	TOBY and DEX	TOBY and Lotep-rednol
and fenestration cavities															

*Suspension.
BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

IV. Pharmacokinetics

There is limited or no data available regarding the pharmacokinetic properties of the eye, ear, nose, and throat (EENT) antibacterial agents.[1-26] The pharmacokinetic parameters of oral doxycycline are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Eye, Ear, Nose, and Throat (EENT) Antibacterials[2]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Doxycycline	Well absorbed (% not reported)	80 to 93	Liver (50)	Renal (35 to 45)	15 to 24

V. Drug Interactions

In general, drug interaction studies have not been completed with the eye, ear, nose, and throat (EENT) antibacterial agents. Major drug interactions with oral doxycycline are listed in Table 8.

Table 8. Major Drug Interactions with the Eye, Ear, Nose, and Throat (EENT) Antibacterials[2]

Generic Name(s)	Interaction	Mechanism
EENT antibacterials (doxycycline)	Acitretin	Concurrent administration of acitretin and doxycycline may increase the risk for development of pseudotumor cerebri. The mechanism of this interaction is unknown.
EENT antibacterials (doxycycline)	Isotretinoin	Concurrent administration of isotretinoin and doxycycline may increase the risk of pseudotumor cerebri. The mechanism of this interaction is unknown.
EENT antibacterials (doxycycline)	Vaccines, live	Doxycycline may decrease the effectiveness of live vaccines when the two are coadministered. Although the exact mechanism of this interaction is unknown, doxycycline may be active against the bacterial strain and decrease the immune response.
EENT antibacterials (doxycycline)	Methotrexate	Concurrent use of doxycycline and methotrexate may result in an increased risk of methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations.
EENT antibacterials (doxycycline)	Oral contraceptives	Pharmacologic effects of oral contraceptives may be decreased by doxycycline in a small unidentifiable subpopulation of patients. Breakthrough bleeding and pregnancy may occur. Doxycycline may alter gut flora and/or cause other gastrointestinal disturbances (vomiting and diarrhea). Lower plasma concentrations of certain contraceptive steroids (because of reduced enterohepatic circulation/reabsorption) may result.
EENT antibacterials (doxycycline)	Penicillins	The antimicrobial effectiveness of penicillins may be decreased. Doxycycline may interfere with the bactericidal activity of penicillins.

VI. Adverse Drug Events

The most common adverse drug events reported with the eye, ear, nose, and throat (EENT) antibacterials are listed in Tables 9 and 10.

Table 9. Adverse Drug Events (%) Reported with the EENT Antibacterials-Single Entity Agents[1-26]

Adverse Event(s)	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Central Nervous System													
Dizziness	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Hallucinations	-	-	-	-	-	-	-	✔	-	-	-	-	-
Headache	-	-	1 to 2	2 to 3	26	-	1 to 4	-	1 to 10	-	≤1	-	-
Paresthesia	-	-	-	-	-	-	-	-	-	-	1	-	-
Vertigo	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Dermatological													
Contact dermatitis	<1	-	-	-	-	-	-	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	-	-	-	1 to 4	-	-
Rash	-	-	-	-	4	-	-	-	-	1 to 4	1	-	-
Gastrointestinal													
Acid indigestion	-	-	-	-	4	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	6	-	-	-	1 to 2	-	-	-	-
Dysgeusia	-	-	-	-	-	-	≥1	-	-	-	-	-	-
Dyspepsia	-	-	-	-	6	-	-	-	1 to 2	-	-	-	-
Nausea	-	-	-	<1	8	-	-	-	1 to 2	-	-	-	-
Taste disturbance	<1	-	-	<10	-	-	1 to 4	-	-	-	-	-	-
Ophthalmic/Otic													
Application site reaction	-	-	-	-	-	-	-	-	-	-	1 to 17	-	-
Blurred vision	-	-	1 to 2	-	-	-	-	-	1 to 2	-	-	-	-
Burning	<1	-	-	✔	-	-	-	✔	1 to 2	1 to 6	✔	✔	-
Chemosis	-	-	-	-	-	-	1 to 4	-	<1	-	-	-	-
Conjunctival epithelial defects	-	-	-	-	-	-	-	✔	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	-	-	-	1 to 4	-	-	1 to 6	-	-	-
Conjunctival redness	-	-	2	<10	-	✔	5 to 10	-	-	1 to 6	✔	✔	✔
Conjunctivitis	-	-	-	-	-	-	-	✔	-	-	-	-	-
Corneal erosion	<1	-	-	-	-	-	-	-	<1	-	-	✔	-
Corneal infiltrates	-	-	-	<1	-	-	-	-	-	-	-	-	-
Corneal staining	-	-	-	<1	-	-	-	-	-	-	-	-	-
Crystals/scales	-	-	-	<10	-	-	-	-	-	-	-	-	-
Decreased vision	-	-	-	<1	-	-	1 to 4	-	-	-	-	-	-
Decreased visual acuity	-	-	-	-	-	-	-	-	-	1 to 6	-	-	-
Diplopia	-	-	-	-	-	-	-	-	<1		-	-	-
Discomfort	-	-	-	✔	-	-	-	-	1 to 2	1 to 6	-	-	-
Dry eyes	<1	-	-	-	-	-	1 to 4	-		1 to 6	✔	-	-
Earache	-	-	-	-	-	-	-	-	-	-	≤1	-	-
Ear pain	-	-	-	-	-	-	≥1	-	-	-	-	-	-
Eye discharge	<1	-	-	-	-	-	1 to 4	-	-	-	-	-	-
Eye irritation	1 to 2	-	1 to 2	-	-	-	≥1	-	-	-	-	-	-

Adverse Event(s)	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Eye pain	-	-	1 to 2	-	-	-	1 to 4	-	-	-	-	-	-
Eye pruritus	-	-	1 to 2	<10	-	-	-	-	-	-	-	-	-
Floaters	-	-	-	-	-	-	-	-	<1	-	-	-	-
Foreign body sensation	-	-	-	<10	-	-	-	-	1 to 3	-	✔	-	-
Hyperemia	-	-	-	-	-	-	-	✔	<1	1 to 6	-	-	-
Irritation	<1	-	-	-	-	✔	-	✔	1 to 2	1 to 6	✔	✔	-
Keratopathy/keratitis	-	-	-	<1	-	-	-	-	-	-	-	-	-
Lid edema	-	-	-	<1	-	-	1 to 4	-	<1	-	✔	-	✔
Lid erythema	-	-	-	-	-	-	-	-	<1	-	-	-	✔
Lid margin crusting	-	-	-	<10	-	-	-	-	-	-	-	-	-
Lid pruritus	-	-	-	-	-	-	-	-	-	-	-	-	✔
Ocular infection	-	-	-	-	-	-	-	-	1 to 2	-	-	✔	-
Ocular pain	-	-	-	-	-	-	-	-	1 to 2	1 to 6	✔	-	-
Otitis media	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-
Papillary conjunctivitis	-	-	-	-	-	-	5 to 10	-	-	-	✔	-	-
Photophobia	-	-	-	<1	-	-	-	-	-	-	-	-	-
Punctate keratitis	<1	-	-	-	-	-	-	-	-	1 to 6	✔	-	-
Stinging	<1	-	-	-	-	-	-	-	1 to 2	1 to 6	✔	✔	-
Tearing	-	-	-	<1	-	-	5 to 10	-	-	1 to 6	✔	-	-
White crystalline precipitates	-	-	-	17	-	-	-	-	-	-	-	-	-
Worsening of conjunctivitis	-	-	-	-	-	-	≥1	-	-	-	-	-	-
Other													
Allergic reactions	-	-	-	<1	-	-	-	✔	-	-	-	-	-
Application site pain	-	-	-	2 to 3	-	-	-	-	-	-	-	-	-
Back ache	-	-	-	-	2	-	-	-	-	-	-	-	-
Back pain	-	-	-	-	3	-	-	-	-	-	-	-	-
Bronchitis	-	-	-	-	3	-	-	-	-	-	-	-	-
Common cold	-	-	-	-	22	-	-	-	-	-	-	-	-
Cough	-	-	-	-	4	-	-	-	-	1 to 4	-	-	-
Fever	-	-	-	-	-	-	-	-	1 to 3	1 to 4	-	-	-
Flu symptoms	-	-	-	-	11	-	-	-	-	-	-		
Fungal ear superinfection	-	-	-	2 to 3	-	-	-	-	-	-	-		
Gum pain	-	-	-	-	<1	-	-	-	-	-	-		
Hypersensitivity	-	-	-	-	-	✔	-	-	<1	-	✔	✔	✔
Infection	-	-	-	-	2	-	-	-	-	1 to 4	-	-	-
Injury	-	-	-	-	5	-	-	-	-	-	-	-	-
Joint pain	-	-	-	-	6	-	-	-	-	-	-	-	-
Menstrual cramp	-	-	-	-	4	-	-	-	-	-	-	-	-
Muscle pain	-	-	-	-	1	-	-	-	-	-	-	-	-
Nasal congestion	<1	-	-	-	-	-	-	-	-	-	-	-	-
Pain	-	-	-	-	4	-	-	-	-	-	-	-	-
Periodontal abscess	-	-	-	-	4	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	1 to 3	1 to 4	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-
Sinus congestion	-	-	-	-	5	-	-	-	-	-	-	-	-

Adverse Event(s)	Single Entity Agents												
	Azithro-mycin	Baci-tracin	Besi-floxacin	Cipro-floxacin	Doxy-cycline	Erythro-mycin	Gati-floxacin	Genta-micin	Levo-floxacin	Moxi-floxacin	Oflox-acin	Sulfacet-amide	Tobra-mycin
Sinus headache	-	-	-	-	4	-	-	-	-	-	-	-	-
Sinusitis	<1	-	-	-	3	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	5	-	-	-	-	-	-	-	-
Taste disturbance	-	-	-	-	-	-	-	-	8 to 10	-	-	-	-
Taste perversion	-	-	-	-	-	-	-	-	-	-	7	-	-
Throat irritation	-	-	-	-	-	-	-	-	1 to 2	-	-	-	-
Tinnitus	-	-	-	-	-	-	-	-	-	1 to 4	-	-	-
Tooth ache	-	-	-	-	7	-	-	-	-	-	-	-	-
Tooth disorder	-	-	-	-	6	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.

Table 10. Adverse Drug Events (%) Reported with the EENT Antibacterials-Combination Products[1-26]

Adverse Events	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trime-thoprim	Sulface-tamide and PRED	TOBY and DEX	TOBY and Lotep-rednol
Central Nervous System															
Dizziness	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	✔	✔	-	-	-	-	-	-	-	-	-	<1	14
Migraines	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Dermatological															
Alopecia	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Edema	✔	-	-	-	-	✔	✔	-	-	✔	-	-	-	-	-
Fungal dermatitis	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Pruritus	✔	-	-	✔	-	✔	✔	-	-	✔	-	-	-	-	-
Rash	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Skin sensitization	-	-	-	-	-	-	-	✔	-	-	✔	-	-	-	-
Urticaria	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal															
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Ophthalmic/Otic			-												
Balance disorder	-	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Blepharitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Burning	-	-	-	-	✔	-	✔	-	-	-	-	✔	✔	-	9
Cataract formation	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔	✔
Chemosis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trime-thoprim	Sulface-tamide and PRED	TOBY and DEX	TOBY and Lotep-rednol
Conjunctival epithelial defects	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctival redness	✔	-	-	-	-	✔	✔	-	-	✔	-	-	✔	✔	✔
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Corneal erosion/ ulceration	-	-	-	-	-	-	-	-	-	-	-	-	✔	-	-
Corneal deposits	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Decreased visual acuity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Discharge	-	-	5.4	-	-	-	-	-	-	-	-	-	-	-	<4
Discomfort	-	-	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dry eyes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear congestion	-	<1	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ear debris	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear discomfort	-	3	✔	-	-	-	-	-	-	-	-	-	-	-	-
Ear erythema	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear infection	-	<1	<1	-	-	-	-	-	-	-	-	-	-	-	-
Ear pain	-	<2	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear precipitate	-	<1	-	-	-	-	-	-	-	-	-	-	-	-	-
Ear pruritus	-	1	<1	-	-	-	-	-	-	-	-	-	-	-	-
Elevated intraocular pressure	-	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	10
Eye irritation	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Floaters	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Foreign body sensation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20
Irritation	-	-	-	-	✔	✔	✔	-	-	-	-	✔	✔	-	-
Keratopathy/ keratitis	✔	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lacrimation disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Lid disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Lid edema	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Lid erythema	-	-	-	-	-	-	✔	-	-	-	-	-	✔	✔	✔

Adverse Events	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trime-thoprim	Sulface-tamide and PRED	TOBY and DEX	TOBY and Lotep-rednol
Lid pruritus	-	-	-	-	-	-	-	-	-	-	-	-	-	✔	✔
Ocular infection	-	-	-	-	✔	-	-	-	✔	-	-	-	✔	✔	✔
Ocular pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Optic nerve damage	-	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	✔
Otitis media	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ototoxicity	-	-	-	-	-	-	✔	✔	✔	✔	✔	-	-	-	-
Photophobia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Posterior subcapsular cataract formation	-	-	-	-	✔	-	✔	-	✔	-	-	-	-	-	-
Pruritus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Punctate keratitis	-	-	-	-	✔	-	-	-	-	-	-	-	✔	-	15
Stinging	-	-	-	-	✔	-	✔	-	-	-	-	✔	✔	✔	9
Tearing	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tympanic membrane disorder	-	-	<1	-	-	-	-	-	-	-	-	-	-	-	-
Vision disorders	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<4
Other															
Allergic reactions	✔	-	✔	-	✔	✔	✔	✔	✔	✔	✔	-	-	-	-
Anaphylaxis	-	-	-	-	-	✔	✔	-	-	-	-	-	-	-	-
Burning/stinging (nasal)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Candidiasis	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-
Cough	-	-	-	✔	-	-	-	-	-	-	-	-	-	-	-
Delayed wound healing	-	-	-	-	✔	-	✔	-	✔	-	-	-	✔	✔	✔
Epistaxis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	✔	-	✔	-	-	-	-	✔	-	✔	✔
Hypertension	-	-	-	-	-	-		--	-		-	-	-	<1	-
Infection (systemic)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nephrotoxicity	-	-	-	-	-	✔	✔	✔	✔	✔	✔	-	-	-	-
Pharyngitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Photosensitivity	-	-	-	-	-	-	-	-	-	-	-	✔	-	-	-
Respiratory disorder	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

Adverse Events	Combination Products														
	BAC and POLY	CIPRO and DEX	CIPRO and fluocin-olone	CIPRO and HYDRO	Genta-micin and PRED	NEO and BAC and POLY	NEO and BAC and POLY and HYDRO	NEO and COL and HYDRO and THON	NEO and POLY and DEX	NEO and POLY and GRAM	NEO and POLY and HYDRO	POLY and Trime-thoprim	Sulface-tamide and PRED	TOBY and DEX	TOBY and Lotep-rednol
Throat irritation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thrombocytopenic purpura	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	✔	-	-	-	-	-	-	-	-	-	-	-	-

✔ Percent not specified.
- Event not reported.
BAC=bacitracin, CIPRO=ciprofloxacin, COL=colistin, DEX=dexamethasone, GRAM=gramicidin, HYDRO=hydrocortisone, NEO=neomycin, POLY=polymyxin B, PRED=prednisolone, THON=thonzonium, TOBY=tobramycin

VII. Dosing and Administration

The usual dosing regimens for the eye, ear, nose, and throat (EENT) antibacterials are listed in Table 11.

Table 11. Usual Dosing Regimens for the EENT Antibacterials[1-26]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Azithromycin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first 2 days and then instill 1 drop in the affected eye(s) once daily for the next 5 days	Bacterial conjunctivitis in children ≥1 year of age: Ophthalmic solution: instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first 2 days and then instill 1 drop in the affected eye(s) once daily for the next 5 days	Ophthalmic solution: 1%
Bacitracin	Ocular infections due to susceptible microorganisms: Ophthalmic ointment: instill ¼ inch to ½ inch ribbon every 3 to 4 hours into conjunctival sac for acute infections, or 2 to 3 times per day for mild-to-moderate infections for 7 to 10 days	Ocular infections due to susceptible microorganisms: Ophthalmic ointment: instill ¼ inch to ½ inch ribbon every 3 to 4 hours into conjunctival sac for acute infections, or 2 to 3 times per day for mild-to-moderate infections for 7 to 10 days	Ophthalmic ointment: 500 units/G
Besifloxacin	Bacterial conjunctivitis: Ophthalmic suspension: instill 1 drop into the affected eye(s) 3 times per day, four to twelve hours apart for 7 days	Bacterial conjunctivitis in children ≥1 year of age: Ophthalmic suspension: instill 1 drop into the affected eye(s) 3 times per day, four to twelve hours apart for 7 days	Ophthalmic suspension: 0.6%
Ciprofloxacin	Acute otitis media: Otic solution: the contents of one single use container should be instilled into the affected ear twice daily for 7 days Bacterial conjunctivitis: Ophthalmic ointment: apply a ½ inch ribbon into the conjunctival sac three times daily for 2 days, then twice daily for 5 days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 hours while awake for 2 days, then every 4 hours while awake for the next 5 days Bacterial corneal ulcers: Ophthalmic solution: instill 2 drops into the affected eye every 15 minutes for the first 6 hours and then every 30	Acute otitis externa in patients ≥1 year of age: Otic solution: the contents of one single use container should be instilled into the affected ear twice daily for 7 days Acute otitis externa in patients ≥6 months of age due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*: Otic suspension: administer Otiprio by a healthcare professional only as a single 0.2 mL (12 mg) administration to the external ear canal of each affected ear Bacterial conjunctivitis: Ophthalmic ointment (patients ≥2 years of age):	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3% Otic solution: 0.2% Otic suspension: 6%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. Thereafter, instill two drops in the affected eye every four hours for the remainder of treatment (14 days)	apply a ½ inch ribbon into the conjunctival sac three times daily for 2 days, then twice daily for 5 days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 hours while awake for 2 days, then every 4 hours while awake for the next 5 days Bacterial corneal ulcers: Ophthalmic solution: instill two drops into the affected eye every 15 minutes for the first six hours and then every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. Thereafter, instill two drops in the affected eye every four hours for the remainder of treatment (14 days) Bilateral otitis media with effusion undergoing tympanostomy tube placement in pediatric patients ≥6 months of age: Otic suspension: administer as a single intratympanic administration of one 0.1 mL (6 mg) dose into each affected ear, following suctioning of middle ear effusion	
Doxycycline	Periodontitis: Tablet: 20 mg twice daily for up to 9 months	Safety and effectiveness have not been established in pediatric patients.	Tablet: 20 mg
Erythromycin base	Bacterial conjunctivitis, bacterial corneal ulcers: Ophthalmic ointment: apply approximately 1 cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection	Bacterial conjunctivitis, bacterial corneal ulcers: Ophthalmic ointment: apply approximately 1 cm to the affected eye(s) up to 6 times daily, depending on the severity of the infection Prophylaxis of ophthalmia neonatorum due to *N gonorrhoeae* or *C trachomatis*: Ophthalmic ointment: apply approximately 1 cm into	Ophthalmic ointment: 5 mg/G

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		each lower conjunctival sac	
Gatifloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 drop into affected eye(s) every 2 hours while awake (up to 8 times daily) for the first day, then two to four times daily for 6 days	Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution (0.5%): instill 1 drop into affected eye(s) every 2 hours while awake (up to 8 times on day 1). Then, instill 1 drop 2 to 4 times daily on days 2 through 7	Ophthalmic solution: 0.5%
Gentamicin	Acute bacterial meibomianitis, bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial corneal ulcers, bacterial dacryocystitis, bacterial keratitis, bacterial keratoconjunctivitis: Ophthalmic ointment: apply approximately ½ inch to the affected eye(s) 2 to 3 times a day Ophthalmic solution: instill 1 or 2 drops into the affected eye every 4 hours. In severe infections, dosage may be increased to as much as 2 drops once every hour.	Acute bacterial meibomianitis, bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial corneal ulcers, bacterial dacryocystitis, bacterial keratitis, bacterial keratoconjunctivitis (patients ≥1 month of age): Ophthalmic ointment: apply approximately ½ inch to the affected eye(s) 2 to 3 times a day Ophthalmic solution: instill 1 or 2 drops into the affected eye every 4 hours. In severe infections, dosage may be increased to as much as 2 drops once every hour.	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%
Levofloxacin	Bacterial conjunctivitis: Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1 to 2 drops every 4 hours while awake (up to 4 times per day) for 5 days	Bacterial conjunctivitis (patients ≥6 years of age): Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 2 hours while awake (up to 8 times per day) for 2 days, then 1 to 2 drops every 4 hours while awake (up to 4 times per day) for 5 days	Ophthalmic solution: 0.5%
Moxifloxacin	Bacterial conjunctivitis: Ophthalmic solution (Moxeza®): instill 1 drop into affected eye(s) two times daily for 7 days Ophthalmic solution (Vigamox®): instill 1 drop into affected eye(s) three times daily for 7 days	Bacterial conjunctivitis (patients ≥4 months of age): Ophthalmic solution (Moxeza®): instill 1 drop into affected eye(s) two times daily for 7 days Bacterial conjunctivitis (birth to 18 years of age): Ophthalmic solution (Vigamox®): instill 1 drop into affected eye(s) three times daily for 7 days	Ophthalmic solution: 0.5%
Ofloxacin	Bacterial conjunctivitis:	Acute otitis media	Ophthalmic solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Ophthalmic solution: instill 1 to 2 drops every 2 to 4 hours into the affected eye(s) for 2 days, then 1 to 2 drops 4 times daily for 5 days Bacterial corneal ulcer: Ophthalmic solution: Days 1 and 2, instill 1 to 2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1 to 2 drops; Days 3 through 7 to 9, instill 1 to 2 drops hourly while awake; Days 7 to 9 through treatment completion, instill 1 to 2 drops 4 times daily Chronic suppurative otitis media (perforated tympanic membranes): Otic solution: instill 10 drops into affected ear(s) twice daily for 14 days Otitis externa: Otic solution: instill 10 drops into affected ear(s) once daily for 7 days	(tympanostomy tubes) (patients ≥1 year of age): Otic solution: instill 5 drops into affected ear(s) twice daily for 10 days Bacterial conjunctivitis (patients ≥1 year of age): Ophthalmic solution: instill 1 to 2 drops every 2 to 4 hours into the affected eye(s) for 2 days, then 1 to 2 drops 4 times daily for 5 days Bacterial corneal ulcer (patients ≥1 year of age): Ophthalmic solution: Days 1 and 2, instill 1 to 2 drops into the affected eye(s) every 30 minutes while awake. Awaken at ~4 and 6 hours after retiring and instill 1 to 2 drops; Days 3 through 7 to 9, instill 1 to 2 drops hourly while awake; Days 7 to 9 through treatment completion, instill 1 to 2 drops 4 times daily Chronic suppurative otitis media (perforated tympanic membranes) (patients ≥12 years of age): Otic solution: instill 10 drops into affected ear(s) twice daily for 14 days Otitis externa: Otic solution (patients ≥6 months to 13 years of age): instill 5 drops into affected ear(s) once daily for 7 days Otic solution (patients ≥13 years of age): instill 10 drops into affected ear(s) once daily for 7 days	0.3% Otic solution: 0.3%
Sulfacetamide	Bacterial conjunctivitis and other superficial ocular infections: Ophthalmic ointment: apply ½ inch ribbon into the conjunctival sac(s) of the affected eye(s) every 3 to 4 hours and at bedtime for 7 to 10	Bacterial conjunctivitis and other superficial ocular infections (patients ≥2 months of age): Ophthalmic ointment: apply ½ inch ribbon into the conjunctival sac(s) of the affected eye(s) every 3 to 4	Ophthalmic ointment: 10% Ophthalmic solution: 10%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 to 3 hours for 7 to 10 days Trachoma: Ophthalmic solution: instill 2 drops into the affected eye(s) every 2 hours	hours and at bedtime for 7 to 10 days Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 to 3 hours for 7 to 10 days Trachoma: Ophthalmic solution: instill 1 to 2 drops into the affected eye(s) every 2 hours	
Tobramycin	Ocular infections due to susceptible microorganisms: Ophthalmic solution (mild to moderate infections): instill 1 to 2 drops into the affected eye(s) every 4 hours Ophthalmic solution (severe infections): instill 2 drops into the affected eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation Ophthalmic ointment (mild to moderate infections): apply ½ inch into the affected eye(s) 2 to 3 times per day Ophthalmic ointment (severe infections): apply ½ inch into the affected eye(s) every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation	Ocular infections due to susceptible microorganisms (patients ≥2 months of age): Ophthalmic solution (mild to moderate infections): instill 1 to 2 drops into the affected eye(s) every 4 hours Ophthalmic solution (severe infections): instill 2 drops into the affected eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation Ophthalmic ointment (mild to moderate infections): apply ½ inch into the affected eye(s) 2 to 3 times per day Ophthalmic ointment (severe infections): apply ½ inch into the affected eye(s) every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%
Combination Products			
Bacitracin and polymyxin B	Bacterial conjunctivitis and bacterial corneal infections: Ophthalmic ointment: apply every 3 to 4 hours for 7 to 10 days, depending on severity of infection	Bacterial conjunctivitis or bacterial corneal infections: Ophthalmic ointment: apply every 3 to 4 hours for 7 to 10 days, depending on severity of infection	Ophthalmic ointment: 500-10KU/G
Ciprofloxacin and dexamethasone	Acute otitis externa: Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days	Acute otitis externa (patients ≥6 months of age): Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days	Otic suspension: 0.3-0.1%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Acute otitis media (tympanostomy tubes) (patients ≥6 months of age): Otic suspension: instill 4 drops into affected ear(s) twice daily for 7 days	
Ciprofloxacin and fluocinolone	Not indicated for use in adult patients.	Acute otitis media with tympanostomy tubes (patients ≥6 months): Otic suspension: instill the contents of one single-dose vial 0.25 mL into the affected ear canal twice daily (approximately every 12 hours) for 7 days	Otic suspension: 0.3-0.025%
Ciprofloxacin and hydrocortisone	Acute otitis externa: Otic suspension: instill 3 drops into affected ear 2 times a day for 7 days	Acute otitis externa (patients ≥1 year of age): Otic suspension: instill 3 drops into affected ear 2 times a day for 7 days	Otic suspension: 0.2-1%
Gentamicin and prednisolone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ½ inch in the conjunctival sac 1 to 3 times per day Ophthalmic suspension: instill 1 drop into affected eye(s) 2 to 4 times daily; dosing frequency may be increased if necessary up to 1 drop every hour	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic ointment: 0.3-0.6% Ophthalmic suspension: 0.3-1%
Neomycin, bacitracin and polymyxin B	Bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial keratitis, and bacterial keratoconjunctivitis: Ophthalmic ointment: apply ointment to affected eye(s) every 3 to 4 hours for 7 to 10 days, depending on the severity of the infection	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic ointment: 3.5 mg-400 units-10,000 units
Neomycin, bacitracin, polymyxin B and hydrocortisone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ointment to the affected eye(s) every 3 to 4 hours, depending on the severity of the condition	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic ointment: 3.5 mg-400 units-10,000 units-1%
Neomycin, colistin, hydrocortisone and thonzonium	Bacterial infections of the external auditory canal and infection of mastoidectomy and fenestration cavities: Otic suspension: instill 5 drops into affected ear(s) 3 to 4 times	Bacterial infections of the external auditory canal and infection of mastoidectomy and fenestration cavities (patients ≥1 year of age): Otic suspension: instill 4	Otic suspension: 3.3-3-10-0.5 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily	drops into affected ear(s) 3 to 4 times daily	
Neomycin, polymyxin B and dexamethasone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment, ophthalmic suspension: instill 1 to 2 drops into affected eye(s). In severe disease, drops may be used hourly. In mild disease, drops may be used up to 4 to 6 times per day.	Steroid-responsive inflammatory conditions and superficial ocular infections (patients ≥2 years of age): Ophthalmic ointment, ophthalmic suspension: instill 1 to 2 drops into affected eye(s). In severe disease, drops may be used hourly. In mild disease, drops may be used up to 4 to 6 times per day.	Ophthalmic ointment: 3.5 mg-10,000 units-0.1% Ophthalmic suspension: 3.5 mg-10,000 units-0.1%
Neomycin, polymyxin B and gramicidin	Bacterial blepharitis, bacterial blepharoconjunctivitis, bacterial conjunctivitis, bacterial keratitis, and bacterial keratoconjunctivitis: Ophthalmic solution: instill 1 to 2 drops into affected eye(s) every 4 hours for 7 to 10 days. In severe infections, dosage may be increased to as much as 2 drops every hour.	Safety and effectiveness have not been established in pediatric patients.	Ophthalmic solution: 1.75 mg-10,000 units-0.025 mg
Neomycin, polymyxin B and hydrocortisone	Bacterial infections of the external auditory canal: Otic solution, otic suspension: instill 4 drops into affected ear(s) 3 to 4 times daily Infection of mastoidectomy and fenestration cavities: Otic suspension: instill 4 drops into affected ear(s) 3 to 4 times daily Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic suspension: instill 1 to 2 drops into affected eye(s) 2 to 4 times per day, or more frequently as required for severe infections	Bacterial infections of the external auditory canal (patients ≥2 years of age): Otic solution, otic suspension: instill 3 drops into affected ear(s) 3 to 4 times daily	Ophthalmic suspension: 3.5 mg-10,000 units-1% Otic solution: 3.5 mg-10,000 units-1% Otic suspension: 3.5 mg-10,000 units-1%
Polymyxin B and trimethoprim	Bacterial blepharoconjunctivitis and bacterial conjunctivitis: Ophthalmic solution: instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Bacterial blepharoconjunctivitis and bacterial conjunctivitis (patients ≥2 months of age): Ophthalmic solution: instill 1 drop in the affected eye(s) every 3 hours for 7 to 10 days	Ophthalmic solution: 10,000 units-0.1%
Sulfacetamide and prednisolone	Steroid-responsive inflammatory conditions and	Steroid-responsive inflammatory conditions	Ophthalmic ointment: 10-0.2%

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	superficial ocular infections: Ophthalmic ointment: apply ½ inch to affected eye(s) 3 to 4 times per day and 1 to 2 times at night Ophthalmic solution: instill 2 drops into affected eye(s) every 4 hours Ophthalmic suspension: instill 2 drops into affected eye(s) every 4 hours during the day and at bedtime	and superficial ocular infections (patients ≥6 years of age): Ophthalmic ointment: apply ½ inch to affected eye(s) 3 to 4 times per day and 1 to 2 times at night Ophthalmic solution: instill 2 drops into affected eye(s) every 4 hours Ophthalmic suspension: instill 2 drops into affected eye(s) every 4 hours during the day and at bedtime	Ophthalmic solution: 10-0.25% Ophthalmic suspension: 10-0.2%
Tobramycin and dexamethasone	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic ointment: apply ½ inch to affected eye(s) up to 3 to 4 times per day Ophthalmic suspension (0.3-0.05%): instill 1 drops into affected eye(s) every 4 to 6 hours Ophthalmic suspension (0.3-0.1%): instill 1 to 2 drops into affected eye(s) every 4 to 6 hours	Steroid-responsive inflammatory conditions and superficial ocular infections (patients ≥2 years of age): Ophthalmic ointment: apply ½ inch to affected eye(s) up to 3 to 4 times per day Ophthalmic suspension (0.3-0.05%): instill 1 drops into affected eye(s) every 4 to 6 hours Ophthalmic suspension (0.3-0.1%): instill 1 to 2 drops into affected eye(s) every 4 to 6 hours	Ophthalmic ointment: 0.3-0.1% Ophthalmic suspension: 0.3-0.05% 0.3-0.1%
Tobramycin and loteprednol	Steroid-responsive inflammatory conditions and superficial ocular infections: Ophthalmic suspension: instill 1 to 2 drops into the affected eye(s) every 4 to 6 hours	In a trial to evaluate the safety and efficacy in pediatric patients aged zero to six years with lid inflammation, tobramycin/loteprednol with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. There were no differences in safety assessments between the treatment groups.	Ophthalmic suspension: 0.3-0.5%

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the eye, ear, nose, and throat (EENT) antibacterials are summarized in Table 12.

Table 12. Comparative Clinical Trials with the EENT Antibacterials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Blepharitis				
John et al.[46] (2008) Azithromycin 1% ophthalmic solution, frequency not reported vs erythromycin ophthalmic ointment, frequency not reported	PRO Patients with chronic mixed anterior blepharitis	N=75 (150 eyes) 8 weeks	Primary: Clinical response Secondary: Not reported	Primary: Sixty-six patients treated with azithromycin ophthalmic solution (132 eyes) showed complete recovery. One patient did not show complete recovery at the completion of the study, but showed an improvement in the blepharitis (Grade 3 to Grade 2) after one month of treatment, and at two months, the blepharitis grade decreased from Grade 2 to Grade 1 and subsequently resolved. The total clinical resolution after 4 weeks was 98.5% with azithromycin and 37.5% with erythromycin. At eight weeks, total clinical resolution was 98.5% for the azithromycin treatment group and 50% for the erythromycin treated group. In the eight patients treated with topical erythromycin ophthalmic ointment, five patients (10 eyes) had unresolved blepharitis with inadequate clinical improvement after one month of treatment. Fifty percent (eight of 16 eyes) of patients treated with erythromycin required eight weeks of treatment as compared to 1.5% (two of 134 eyes) of patients treated with azithromycin. The average initial blepharitis grade of patients and the average blepharitis grade taken at four and eight week intervals of treatment showed that patients treated with azithromycin had a better clinical response during a shorter treatment duration as compared to patients treated with erythromycin. The results after four weeks of treatment was statistically significant in favor of azithromycin (P=0.0237). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Blepharokeratoconjunctivitis				
Rhee et al.[47] (2007) TOBY and DEX 0.3-0.1% ophthalmic solution BID vs TOBY and loteprednol 0.3-0.5% ophthalmic solution BID	DB, RCT Patients with moderate blepharokerato-conjunctivitis in at least 1 eye	N=40 (40 eyes) 3 to 5 days	Primary: Ocular signs and symptoms Secondary: Not reported	Primary: TOBY and DEX significantly decreased clinical signs of ocular inflammation, including blepharitis (P=0.017), conjunctivitis (P=0.013), ocular discharge (P=0.025) and total posttreatment symptom scores (P<0.05) compared to TOBY and loteprednol. Mean keratitis scores did not differ between the treatment groups (P=0.065). Mean total ocular scores for TOBY and DEX were greater than those for TOBY and loteprednol at the post-visit evaluation. No patients in either treatment group required additional therapy or a longer course of treatment. No adverse events were reported in any patient in either treatment group. Secondary: Not reported
White et al.[48] (2008) TOBY and DEX 0.3-0.1% ophthalmic solution QID for 3 to 5 days vs TOBY and loteprednol 0.3-0.5% ophthalmic solution QID for 3 to 5 days	MC, RCT Patients with blepharokerato-conjunctivitis	N=276 15 days	Primary: Change from baseline to day 15 for ocular signs and symptoms and investigator's global assessment Secondary: Percentage of eyes that were cured or not cured based on the investigator's global assessment; change from baseline to day seven and day three in the signs/ symptoms composite	Primary: At day 15, the mean change from baseline in the signs and symptoms composite score for the ITT population was -15.2 for patients treated with TOBY and loteprednol and -15.6 for TOBY and DEX-treated patients, representing a 78% reduction from baseline for both treatments. There was no significant difference between the treatment groups. At day three and day seven, the mean change from baseline in the signs and symptoms composite score for the ITT population was -7.1 and -12.3 for TOBY and loteprednol-treated patients and -7.6 and -13.2 for TOBY and DEX-treated patients. There was no significant difference between the treatment groups. In the per protocol analysis, the mean change from baseline in the signs and symptoms composite score was -7.2 and -7.4 on day 3, -13.0 and -13.2 on day 7, and -15.8 and -15.7 on day 15 for TOBY and loteprednol-treated patients and TOBY and DEX-treated patients, respectively. There was no significant difference between the treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			score; change from baseline to each visit in the signs composite score and symptoms composite score; adverse events	Based on the investigator global assessment, the percentage of TOBY and loteprednol and TOBY and DEX study eyes considered 'cured' was 2.2 and 0.7% at day three, 20.1 and 16.5% at day seven, and 43.6 and 40.9% at day 15, respectively. There was no significant difference between the treatment groups. The mean change from baseline in the signs composite score for the ITT population for TOBY and loteprednol and TOBY and DEX was -3.3and -3.4 at day three, -6.1 and -6.4 at day seven, and -7.4 and -7.6 at day 15, respectively. There was no significant difference between the treatment groups. The mean change from baseline in the symptoms composite score for TOBY and loteprednol and TOBY and DEX was -3.8 and -4.2 at day three, -6.2 and -6.8 at day seven, and -7.8 and -8.0 at day 15, respectively. There was no significant difference between the treatment groups. There was no significant difference in the mean change from baseline in the blepharitis, conjunctivitis, and keratitis signs composite scores for the ITT population. A total of four patients (2.9%) in each treatment group reported a non-ocular treatment-emergent adverse event, with one subject in the TOBY and DEX group reporting a serious adverse event. Most non-ocular adverse events were considered mild to moderate in severity, with the exception of hypertension in the TOBY and DEX group and one instance of headache in the TOBY and loteprednol group, which were considered severe. A total of four patients (2.9%) in the TOBY and loteprednol group and nine patients (6.5%) in the TOBY and DEX group reported treatment-emergent ocular adverse events in the study eye. All treatment-emergent ocular adverse events were considered mild to moderate in severity, and most were considered related to the treatment. There were no clinically significant changes in the proportion of eyes with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				'none', 'minimal/trace', 'mild', or 'moderate' cataract over the course of the study. Patients treated with TOBY and DEX experienced a statistically significant increase in IOP compared to patients treated with TOBY and loteprednol at day seven (0.6 vs -0.1, P=0.0339), at day 15 (1.0 vs -0.1, P=0.0091), and overall (2.3 vs 1.6, P=0.0208).
Chen et al.[49] (2012) TOBY and loteprednol 0.3-0.5% ophthalmic suspension QID for 2 weeks vs TOBY and DEX 0.3-0.1% ophthalmic suspension QID for 2 weeks	MC, PG, SB, RCT Chinese patients ≥18 years of age with ocular inflammation associated with blepharokerato-conjunctivitis	N=308 15 days	Primary: Change in baseline in the signs and symptoms composite score to visit four (day 15) Secondary: Safety, biomicroscopy findings, changes in visual acuity and IOP	Primary: A significant change from baseline in composite signs and symptoms was seen with both treatments at each follow-up visit (P< 0.0001). The mean±SD change from baseline at visit four was -11.63±4.56 and -12.41±4.71 with TOBY and loteprednol and TOBY and DEX, respectively. The upper bound of the 90% CI for the difference was less than the prespecified NI margin. Secondary: Comparable results were found for secondary efficacy outcomes. Patients treated with TOBY and DEX experienced a significantly greater increase in mean change from baseline in IOP compared to patients treated with TOBY and loteprednol at all follow-up visits (P≤0.0186) and nearly twice as many IOP evaluations ≥5 mm Hg (P=0.0020).
Conjunctivitis				
Abelson et al.[50] (2008) Azithromycin 1% ophthalmic solution 1 drop BID on days 1 and 2, followed by QD on days 3 through 5 vs placebo	Phase 3 DB, MC, PC, PG, RCT Patients ≥1 year of age with a positive clinical diagnosis of bacterial conjunctivitis with signs and symptoms present for less than three days and a best-corrected visual acuity score of	N=685 5 days	Primary: Clinical resolution at the TOC visit (visit three on day six or seven) Secondary: Bacterial eradication at visit three, as indicated by the absence of bacterial growth and incidence of adverse events	Primary: Clinical resolution rates at visit three were significantly higher with azithromycin compared to placebo (63.1 vs 49.7%, respectively; P=0.03). Secondary: Bacterial eradication rates measured at visit three were significantly higher with azithromycin compared to placebo (88.5 vs 66.4%; P<0.001). The rate of overall adverse events see with azithromycin was 12.3% compared to 12.0% with placebo, with the most common adverse effects seen including conjunctival chemosis, lid swelling, and other lid events (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥20/100 in each eye			
Abelson et al.[51] (2007) Azithromycin 1% ophthalmic solution BID on days 1 and 2, followed by QD for 3 days vs TOBY 0.3% ophthalmic solution QID for 5 days	AC, DB, RCT Patients ≥1 year of age with purulent conjunctival discharge and conjunctival or palpebral injection of no more than 3 days' duration	N=743 5 days	Primary: Clinical resolution of the signs and symptoms of infective bacterial conjunctivitis Secondary: Bacterial eradication	Primary: Treatment with 1% azithromycin achieved clinical resolution in 79.9% of participants; treatment with TOBY achieved clinical resolution in 78.3% of participants (P=0.783). At day three, 93.9% of infections that were treated with 1% azithromycin were resolved or improved. There were no statistically significant differences between the treatment groups (P=0.949). Secondary: Treatment with 1% azithromycin achieved bacterial eradication in 88.1% of participants. Treatment with TOBY achieved bacterial eradication in 94.3% (P=0.073).
Protzko et al.[52] (2007) Azithromycin 1% ophthalmic solution BID on days 1 and 2, followed by QD for 3 days vs TOBY 0.3% ophthalmic solution QID for 5 days	AC, DB, RCT Patients ≥1 year of age with a diagnosis of bacterial conjunctivitis of less than 3 days' onset	N=743 5 days	Primary: Safety and tolerability Secondary: Not reported	Primary: There was no significant difference in the frequency of adverse events between the two treatment groups. Among all adverse events reported, 3% were deemed treatment-related in the 1% azithromycin group and 5.6% in the TOBY group. The most frequently observed ocular adverse events in the overall study population were eye irritation (1.9%), conjunctival hyperemia (1.1%), and worsening conjunctivitis (1.1%). The percentage of participants with a clinically significant decline in visual acuity of three lines or more at any visit (schedule or unscheduled) was 0.8% in either treatment arm. More than 96% of participants had no change in visual acuity at any visit during the course of treatment. Few patients experienced any worsening of ophthalmic signs. The most frequent treatment-emergent outcome was swelling of the eyelid, which was seen in 3.3% of participants in each treatment group. Other findings in the conjunctiva, lids, and cornea were equally distributed at relatively low frequencies in both treatment groups. The treatments were equally capable of eradicating the predominant Gram-negative and Gram-positive pathogens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Cochereau et al.[53] (2007) Azithromycin 1.5% ophthalmic solution 1 drop BID for 3 days vs TOBY 0.3% ophthalmic solution 1 drop every 2 hours up to 8 times a day for 2 days, followed by QID for 5 days	MC, NI, PG, RCT Patients ≥1 day old with a diagnosis of purulent bacterial conjunctivitis defined as bulbar injection and purulent discharge	N=1,043 9 days	Primary: Clinical efficacy, microbiological assessment and safety Secondary: Not reported	Primary: Clinical efficacy, measured as the number of patients cured on day nine, showed that azithromycin was non inferior to TOBY (87.8 vs 89.4%, respectively; 95% CI, -7.5 to 4.4). NI was also found for all efficacy criteria at assessment days three and nine (95% CI, -5.3 to 8.3 and -6.6 to 3.0, respectively). Additionally, azithromycin showed a statistically higher cure rate than TOBY (29.8 vs 18.6%, respectively; P value not reported). The rate of bacteriological resolution for azithromycin was found to be non-inferior to TOBY at both day three (85.2 vs 83.8%; 95% CI, not reported) and day nine (92.8 vs 94.6%; 95% CI, not reported). Adverse events reported were mile to moderate. Four patients presented with treatment-related adverse events, three from the azithromycin group (two with burning and one with burning/foreign body sensation) and one from the TOBY group for discharge. Secondary: Not reported
Bremond-Gignac et al.[54] (2014) Azithromycin 1.5% ophthalmic solution one drop BID for 3 days vs TOBY 0.3% ophthalmic solution one to two drops every 2 hours up to	MC, RCT, SB Children (from 1 day to 18 years old, average age of 3 years) with purulent bacterial conjunctivitis, defined by mild to severe bulbar conjunctival injection and purulent discharge in at least one eye	N=203 7 days	Primary: Clinical cure (as defined by the absence of bulbar conjunctival injection and purulent discharge in the worse eye on day 3) Secondary: Clinical cure on day 7, other ocular signs, symptoms of bacterial	Primary: On day 3, the clinical sure rate was higher in the azithromycin group compared with the TOBY group (47.1 vs 28.7%, respectively; P=0.013). Secondary: On day 7 there was no significant difference in clinical cure rates between treatment groups (89.2 vs 78.2%, respectively; P=0.077), and non-inferiority of azithromycin to tobramycin was demonstrated. Improvements of other ocular signs (folliculo-papillary reaction, eyelid erythema, eyelid swelling) were noted on days 3 and 7, but were not significantly different between groups (Day 3: P=0.067, Day 7: P=0.172).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
8 times a day for 2 days, followed by one drop QID for 5 days			conjunctivitis scored on a four-point ordinal scale	
Gigliotti et al.[55] (abstract) (1984) BAC and POLY ophthalmic ointment QID for seven days vs placebo	DB, RCT Patients 1 month to 18 years of age with acute conjunctivitis	N=102 10 days	Primary: Clinical cure rate and bacterial pathogen eradication Secondary: Not reported	Primary: During days three through five, significantly more patients treated with BAC and POLY were clinically cured compared to patients treated with placebo (62 vs 28%, respectively; P<0.02). However, on days eight through ten, the difference between the treatments was not significant (91 vs 72%; P value not reported). It was found that the bacterial pathogen was eradicated in significantly more patients in the treatment group compared to the placebo group on days three to five, as well as on days eight to 10 (72 vs 19% and 79 vs 31%, respectively; P<0.001 for both). Secondary: Not reported
Sheikh et al.[56] (2006) BAC and POLY ophthalmic ointment 500-10,000 units/g vs CIPRO 0.3% vs chloramphenicol 0.5%* vs	MA Patients ≥1 month of age with acute bacterial conjunctivitis and symptoms of less than four weeks duration	N=1,034 Duration not specified	Primary: Early clinical remission, early microbiological remission, late clinical remission and late microbiological remission Secondary: Not reported	Primary: When BAC and POLY was compared to vehicle with regard to early clinical remission at days three through five, BAC and POLY was favored (RR, 2.20; 95% CI, 1.19 to 4.06). When BAC and POLY was compared to vehicle with regard to microbiological remission during days three through five, BAC and POLY was favored (RR, 3.76; 95% CI, 1.77 to 8.00). CIPRO was also favored when compared to vehicle with regard to early microbiological remission at day three (RR, 1.59; 95% CI, 1.21 to 2.08). BAC and POLY was favored over vehicle with regard to late clinical remission at days eight to 10 (RR, 1.27; 95% CI, 1.00 to 1.61) as well as for late microbiological remission in days eight through ten (RR, 2.54; 95% CI, 1.48 to 4.37). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fusidic acid gel 1%* vs norfloxacin 0.3%* vs vehicle				
DeLeon et al.[57] (2012) Besifloxacin 0.6% ophthalmic suspension BID for 3 days vs placebo	DB, MC, PC, PG, RCT Patients ≥1 years of age with bacterial conjunctivitis	N=474 7 days	Primary: Bacterial eradication and clinical resolution at day 4/5 Secondary: Bacterial eradication and clinical resolution at day seven, safety	Primary: Bacterial eradication and clinical resolution rates were significantly higher with besifloxacin compared to placebo (115/135 [85.2%] vs 77/141 [54.6%]; P<0.001, and 89/135 [65.9%] vs 62/141 [44.0%]; P<0.001, respectively) at day 4/5. Secondary: Rates of bacterial eradication continued to be significantly greater with besifloxacin (115/135 [85.2%] vs 91/141 [64.5%], respectively; P<0.001) at day 7±1; however, the rates of clinical resolution did not differ between the two treatments (103/135 [76.3%] and 94/141 [66.7%]; P=0.209) at this visit. Clinical resolution and bacterial eradication with Gram-positive or Gram-negative organisms were consistent with the overall findings. All adverse events with both treatments were of mild or moderate severity and were considered unrelated to the treatment.
Karpecki et al.[58] (2009) Besifloxacin 0.6% ophthalmic suspension TID for 5 days vs placebo	DB, MC, PC, RCT Patients ≥1 year of age with a diagnosis of bacterial conjunctivitis	N=269 8 days	Primary: Clinical resolution and eradication of bacterial infection Secondary: Clinical resolution of conjunctivitis at visit two; eradication of baseline bacterial	Primary: Clinical resolution of baseline conjunctivitis at visit three was significantly better in patients who received besifloxacin compared to placebo (73.3 vs 43.1%, respectively; P<0.001). Eradication of bacterial infection at visit three also was significantly greater in the besifloxacin group compared to placebo (88.3 vs 60.3%; P<0.001). Secondary: There was no difference in clinical resolution of conjunctivitis at visit two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			infection at visit two; and improvements in investigators' ratings of individual signs and symptoms, global change in clinical signs and symptoms, microbiologic outcomes, and clinical outcomes	between the treatment groups (33.3 vs 17.2%, respectively). Eradication of bacterial infection at visit 2 was significantly greater in the besifloxacin group compared to placebo (90.0 vs 46.6%; P<0.001). Investigators' ratings of individual signs and symptoms were significantly better with besifloxacin compared to placebo at visit two (ocular discharge; P=0.008, bulbar conjunctival injection; P=0.014) and visit three (P=0.003 and P=0.013, respectively), as were investigators' ratings of global changes in signs and symptoms at visit two (P=0.004) and visit three (P<0.001). There was no difference between the besifloxacin and placebo groups in the cumulative frequency of patients with at least one adverse event (50.4 and 53.0%, respectively). Most adverse events in both treatment groups were of mild or moderate severity (98.7 and 100%), and most were considered unrelated or unlikely to be related to treatment (50 and 53.9%).
Tepedino et al.[59] (2009) Besifloxacin 0.6% ophthalmic suspension QID for 5 days vs placebo	DB, MC, PC, RCT Patients ≥1 year of age with bacterial conjunctivitis	N=390 9 days	Primary: Clinical resolution and microbiological eradication of baseline infection at visit two (day five) Secondary: Clinical resolution and microbial eradication at visit three (day eight or nine), individual clinical outcomes at follow-up visits, and safety	Primary: Clinical resolution in the baseline-designated study eye was significantly higher in the besifloxacin ophthalmic suspension group than in the vehicle group at visit (45.2 vs 33.0%; P=0.0084). Microbial eradication in the baseline-designated study eye was significantly greater with besifloxacin ophthalmic suspension treatment group than with vehicle at visit (91.5 and 59.7%, respectively; P<0.0001). Secondary: Clinical resolution in the baseline-designated study eye was significantly higher in the besifloxacin ophthalmic suspension group than in the vehicle group at visit three (84.4 vs 69.1%; P=0.0011). Microbial eradication in the baseline-designated study eye was significantly greater with besifloxacin ophthalmic suspension treatment group than with vehicle at visit three (88.4 and 71.7%, respectively; P<0.0001). The percentage of patients treated with besifloxacin ophthalmic

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				suspension who had resolution of ocular discharge was significantly greater at visit two (73.9 vs 57.6%; P=0.0012) and at visit three (93.0 vs 79.1%; P=0.0002) compared to those treated with vehicle. Significantly greater percentages of patients treated with besifloxacin ophthalmic suspension had normal bulbar conjunctival injection than those treated with vehicle at both visit two (52.3 vs 36.1%; P=0.0007) and visit three (84.9 vs 70.7%; P=0.0011). At visit two, 39.2 and 29.3% of patients randomized to besifloxacin ophthalmic suspension or vehicle, respectively, were considered cured by the investigator (P=0.02). At visit three, the respective rates were 83.9 and 66.0% (P=0.0002). Treatment with besifloxacin ophthalmic suspension was well tolerated. The majority of ocular adverse events were mild to moderate in severity. A significantly greater percentage of eyes treated with vehicle experienced at least one ocular adverse event compared to those treated with besifloxacin ophthalmic suspension (13.9 vs 9.2%; P=0.0047).
Silverstein et al.[60] (2011) Besifloxacin 0.6% ophthalmic suspension 1 drop BID for 3 days vs placebo	DB, MC, PG, PRO, RCT Patients ≥1 year of age with a clinical diagnosis of acute bacterial conjunctivitis with purulent discharge, crusty or sticky eyelids ocular surface redness and a minimum of grade one severity for both discharge and bulbar conjunctival	N=202 7 days	Primary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit two Secondary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit three and individual clinical outcomes at the follow- up visits	Primary: At visit two, clinical resolution of conjunctivitis in the study eye was significantly higher with besifloxacin compared to placebo (69.8 vs 37.5%, respectively; P<0.001). The eradication of bacterial infection at visit two occurred in significantly more patients with besifloxacin compared to placebo (86.8 vs 57.1%; P<0.001). Secondary: Rates of eradication of bacterial infection in the study eye at visit three were significantly greater with besifloxacin compared to placebo (86.8 vs 69.6%, respectively; P=0.038). Rates of clinical resolution of bacterial conjunctivitis at visit three did not differ significantly between besifloxacin and placebo (73.6 vs 66.1%; P=0.717).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	injection in ≥1 eye			At visit two, the percentage of patients treated with besifloxacin who had resolution of ocular discharge was significantly greater compared to those who received placebo (83.0 vs 55.4%, respectively; P=0.002), but not at visit three (86.8 vs 76.8%; P value not reported). The proportion of patients treated with besifloxacin who had resolution of bulbar conjunctival injection was significantly greater compared to patients receiving placebo at visit two (77.4 vs 44.6%; P<0.001), but not at visit three (83.0 vs 73.2%; P value not reported).
Silverstein et al.[61] (2012) Besifloxacin 0.6% ophthalmic suspension 1 drop BID or TID vs placebo or moxifloxacin 0.5% ophthalmic solution 1 drop TID	Post-hoc analysis of 4 trials Patients ≥1 year of age with a clinical diagnosis of bacterial conjunctivitis as evidenced by a grade one or greater severity of both purulent ocular discharge and bulbar conjunctival injection in at least one eye, had culture-confirmed *P aeruginosa* infections and had pinhole visual acuity of ≥20/200	N=9 3 to 5 days	Primary: Clinical resolution and bacterial eradication of the baseline bacterial infection at visit two or three Secondary: Ocular and non-ocular adverse events, changes in visual acuity and biomicroscopy and ophthalmoscopy findings at follow-up visits	Primary: Of a total of 2,859 patients across of the four trials, nine patients had culture-confirmed *P aeruginosa* infections. Five of these patients received besifloxacin, all of whom had bacterial eradication of the baseline infections at visits two and three. Clinical resolution was reported in two of these patients by visit two and in four of these patients by visit three. Data on patients who received vehicle or moxifloxacin was not reported. Secondary: No adverse events were reported in the five patients who received besifloxacin. There were no clinically meaningful changes in visual acuity or any biomicroscopy or ophthalmoscopy findings.
Comstock et al.[62] (2010) Besifloxacin 0.6% ophthalmic suspension 1 drop	Post-hoc analysis of 3 trials Patients 1 to 17 years of age with bacterial	N=815 8 to 9 days	Primary: Clinical resolution and microbial eradication Secondary:	Primary: *PC trials* The percentage of eyes with clinical resolution was significantly higher (P<0.05) in the besifloxacin group than in the placebo group at visit two (53.7 vs 41.3%) and visit three (88.1 vs 73.0%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TID daily for 5 days vs moxifloxacin 0.5% ophthalmic solution (1 trial) vs placebo (2 trials)	conjunctivitis		Not reported	Microbial eradication was significantly better (P<0.05) with besifloxacin than with placebo at visit two (85.8 vs 56.3%) and visit three (82.8 vs 68.3%). *Moxifloxacin controlled trial* High rates of clinical resolution and microbial eradication were seen in both the besifloxacin- and moxifloxacin-treated groups, with rates ranging from 69.9 to 89.8% for clinical resolution and from 66.7 to 94.2% for microbial eradication. There were no significant differences between the two treatments. *Adverse events* The overall incidence of adverse events was similar between treatment groups (besifloxacin 11.0%; placebo 14.2%; moxifloxacin 10.6%). Rates of individual ocular adverse events were low in all treatment groups. The most commonly reported ocular adverse events among all besifloxacin-treated eyes, i.e. conjunctivitis (2.9%), bacterial conjunctivitis (2.1 %), and eye pain (1.8%), were consistent with the underlying condition being treated. Secondary: Not reported
McDonald et al.[63] (2009) Besifloxacin 0.6% ophthalmic suspension TID for 5 days vs moxifloxacin 0.5% ophthalmic solution TID for 5 days	DB, MC, PG, RCT Patients ≥1 year of age with bacterial conjunctivitis	N=1,161 8 days	Primary: Clinical resolution and microbial eradication of baseline bacterial infection on day five in patients with culture-confirmed bacterial conjunctivitis Secondary: Clinical resolution and microbial eradication on day	Primary: On day five in the modified ITT population (culture confirmed), 58.3 and 59.4% of patients treated with besifloxacin and moxifloxacin had clinical resolution, respectively (P=0.6520). Secondary: On day eight, clinical resolution was seen in 84.5 and 84.0% of patients treated with besifloxacin and moxifloxacin, respectively (P=0.5014). Non-inferiority was also demonstrated in the ITT population for clinical resolution. Besifloxacin was shown to be non-inferior to moxifloxacin with regard to microbial eradication in the modified ITT population. On day five, microbial eradication occurred in 93.3% of patients receiving besifloxacin and 91.1% of patients receiving moxifloxacin (P=0.1238). On day eight,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eight, individual clinical outcomes, microbial and clinical outcomes by bacterial species, and safety	87.3% and 84.7 of patients treated with besifloxacin or moxifloxacin, respectively, had microbial eradication (P=0.0608). According to the investigator's global assessment of response, 56.7 and 57.3% of patients treated with besifloxacin and moxifloxacin, respectively, were considered cured on day five (P=0.9303). A greater percentage of patients were considered to be cured on day 8: 84.9% of patients receiving besifloxacin compared to 84.7% of patients receiving moxifloxacin (P>0.9999). Similar results were noted in the ITT population for the investigator's global assessment. Clinical resolution and microbial eradication by baseline infection with either gram-positive or gram-negative organisms did not differ significantly from the overall study results. There were no differences between groups in the frequency of eyes that had at least one ocular adverse events (12.0% for besifloxacin and 14.0% for moxifloxacin; P=0.2238). Only eye irritation was statistically different between treatment groups, occurring in 0.3% of eyes treated with besifloxacin and in 1.4% treated with moxifloxacin (P=0.0201).
Leibowitz et al.[64] (abstract) (1991) CIPRO 0.3% ophthalmic solution vs TOBY 0.3% ophthalmic solution vs placebo	2 MC, PRO, RCT Patients with bacterial conjunctivitis	N=288 Duration not specified	Primary: Antibacterial efficacy and eradication of bacterial pathogens Secondary: Not reported	Primary: In one trial, CIPRO was shown to be significantly more effective than placebo (P<0.001) and eradicated or reduced the various bacterial pathogens in more patients when compared to placebo (93.6 vs 59.5%; P value not reported). In a second trial CIPRO and TOBY were found to be equally effective in antibacterial efficacy (94.5 vs 91.9%; P value not reported). Secondary: Not reported
Gross et al.[65] (1997)	DB, MC, RCT	N=257	Primary: Microbiological	Primary: Microbiological eradication on follow-up was observed in 90.1% of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 3 to 7 days vs TOBY 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 3 to 7 days	Children 0 to 12 years of age with a diagnosis of acute (<7 days) bacterial conjunctivitis	7 days	efficacy, physician's impression of condition, and severity of signs/symptoms Secondary: Not reported	ciprofloxacin group and 84.3% of the TOBY group (P=0.29). Microbiological reduction was observed in 2.8% of the ciprofloxacin group and 2.9% of the TOBY group (P=0.29). No significant treatment difference was found for physician's judgment on day three (P=0.63) or day seven (P=0.60). Physicians judged 87.0% of the ciprofloxacin patients and 89.9% of the TOBY patients clinically cured on day seven. No significant treatment differences were found for the three cardinal signs of bacterial conjunctivitis. The changes for erythema/swelling, discharge/exudate, and bulbar conjunctiva between day one and days three and seven were comparable (P>0.05). There were no significant differences between treatment groups for the other signs and symptoms evaluated (P>0.05). Ciprofloxacin and TOBY were safe and well tolerated. No serious adverse events that were determined to be related to the study medications occurred during the study. No clinically significant differences in visual acuity were observed between the two treatment groups. Secondary: Not reported
Yee et al.[66] (2005) Gatifloxacin 0.3% ophthalmic solution BID for 5 days vs gatifloxacin 0.3% ophthalmic solution QID for 5 days	MC, TCT Patients ≥5 years of age and ≥10 kg with bacterial conjunctivitis, as well as at least +1 (mild) bulbar conjunctival hyperemia and at least +1 (mild) discharge in the same eye (5-point	N=104 5 days	Primary: Clinical cure on day five in the ITT population Secondary: Clinical cure on day five in the per protocol population, safety	Primary: The clinical cure rates in the BID group were 86.5 and 71.2% in the QID group on day five (95% CI, -0.03 to 30.80; P=0.096). Secondary: Clinical cure rates at day five in the per protocol population were 95.5% in the BID group and 85.7% in the QID group (95% CI, -7.57 to 27.05; P=0.294). No serious adverse events were reported in either group. The most common adverse event was conjunctivitis. There were no significant differences in the incidence of any adverse event (P>0.999). The overall incidence of adverse events was the same (9.6%) in both the BID and the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	scale)			QID groups (P>0.999).
Hwang et al.[67] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 to 2, followed by every 4 hours on days 3 to 5 vs placebo	DB, MC, PC, RCT Patients ≥2 years of age with bacterial conjunctivitis, characterized by purulent ocular discharge and redness in at least one eye	N=117 5 days	Primary: Antimicrobial efficacy, clinical efficacy, resolution of ocular signs and symptoms, safety Secondary: Not reported	Primary: At each visit, approximately twice as many patients in the levofloxacin group as in the placebo group achieved microbial eradication (P<0.001). In the levofloxacin treatment group, 88% of children (two to 11 years of age) achieved microbial eradication, compared to 24% of children receiving placebo (P<0.001). Corresponding microbial eradication rates in adults were 90 vs 65%, respectively (P=0.007). There was no significant difference in microbial eradication rates between treatment groups in the subset of adolescents. Clinical cure rates were significantly greater in the levofloxacin treatment group than in the placebo group at both the final visit (P=0.020) and at end point (P=0.026). Subgroup analysis by age revealed a significant difference in favor of levofloxacin in children; clinical cure rates were 88 and 53% for children receiving 0.5% levofloxacin and placebo, respectively (P=0.034). Resolution rates for ocular signs and symptoms were higher in the levofloxacin treatment group than in the placebo group at all study visits. Statistically significant differences favoring levofloxacin were observed for resolution of the ocular signs of conjunctival discharge (P=0.027), bulbar conjunctival injection (P=0.029), and palpebral conjunctival injection (P=0.018), and for the ocular symptoms of burning/stinging (P=0.008), itching (P=0.037), and photophobia (P=0.023). There were no significant differences between treatment groups in the incidence of overall adverse events or treatment related events. Most adverse events were mild to moderate in severity. Conjunctivitis, primarily in the non-study eye, was the most common overall adverse event. Treatment related adverse events were predominantly ocular and occurred in 9% and 6% of patients in the levofloxacin and placebo treatment groups, respectively. The most common treatment related adverse events in the levofloxacin treatment group were transient burning (2.4%) and transient decreased vision (2.4%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Lichtenstein et al.[68] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 and 2, followed by every 4 hours on days 3 through 5 vs ofloxacin 0.5% ophthalmic solution administered every 2 hours on days 1 and 2, followed by every 4 hours on days 3 through 5 vs placebo	Subset analysis of 2 trials Pediatric patients aged 1 to 16 years old with bacterial conjunctivitis	N=167 10 days	Primary: Microbial eradication, physicians' clinical impression of change from baseline in cardinal signs, change from baseline in ocular signs/symptoms, and safety Secondary: Not reported	Primary: The five-day dosing regimen with 0.5% levofloxacin ophthalmic solution demonstrated microbial eradication rates in pediatric patients that were greater than those observed with either 0.3% ofloxacin ophthalmic solution or placebo treatment. In children (two to 11 years of age), this finding was statistically significant in favor of 0.5% levofloxacin compared to 0.3% ofloxacin (87 vs 62%; P≤0.032) and for 0.5% levofloxacin compared to placebo (88 vs 24%; P<0.001). Treatment with 0.5% levofloxacin ophthalmic solution resulted in a clinical cure rate in pediatric patients (81%) that was similar to that achieved with 0.3% ofloxacin ophthalmic solution (86%). Treatment with 0.5% levofloxacin ophthalmic solution resulted in a clinical cure rate in pediatric patients (89%) that was greater than that attained with placebo treatment (50%). This finding was statistically significant in children (two to 11 years) with clinical cure rates of 88% with 0.5% levofloxacin vs 53% with placebo (P≤0.034). Physicians judged 99% of pediatric patients treated with 0.5% levofloxacin to be resolved or improved compared to 94% of patients in the 0.3% ofloxacin treatment group and 85% of patients in the placebo group. Resolution rates from baseline in ocular signs and symptoms were higher in patients who received active drug compared to placebo; resolution rates achieved in the 0.5% levofloxacin and the 0.3% ofloxacin treatment groups were similar. All three treatments were safe and well tolerated. There were no differences between treatment groups in the incidence of adverse events, and no serious adverse events were reported in pediatric patients. Overall, the most common ocular and non-ocular adverse events in the active-treatment groups, regardless of relationship to study medication, were transient burning (2%) and fever (3%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Szaflik et al.[69] (2009) Levofloxacin 0.5% ophthalmic solution TID for 5 days vs levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours for the next 3 days	OL, RCT Patients ≥18 years of age with clinical diagnosis of bacterial conjunctivitis and the presence of three cardinal signs (purulent conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection)	N=120 7 days	Primary: Clinical cure Secondary: Microbiological eradication	Patients' disposition There was no significant difference between the groups in the frequency of patients with a resolved clinical outcome (RR, 1.85; 95% CI, 0.50 to 6.87; P=0.48). Secondary: There was no significant difference between groups in the frequency of patients with a resolved microbiology outcome (RR, 1.39; 95% CI, 0.25 to 7.85; P=1.00). No adverse events were reported in the studied groups. No significant changes in the patients' body temperature, blood pressure, and pulse were observed during the study.
Schwab et al.[70] (2003) Levofloxacin 0.5% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours on days 3 through 5 vs ofloxacin 0.3% ophthalmic solution administered every 2 hours for the first 2 days, followed by every 4 hours on	AC, DB, RCT Patients ≥1 year of age with a clinical diagnosis of bacterial conjunctivitis, characteristic purulent conjunctival discharge, and redness in at least one eye	N=423 6 to 10 days	Primary: Microbial eradication and clinical cure Secondary: Resolution of ocular signs and symptoms	Primary: A significantly greater proportion of patients receiving 0.5% levofloxacin experienced microbial eradication compared to patients receiving 0.3% ofloxacin at both the final visit (89 vs 80%; P=0.034) and at end point (90 vs 81%; P=0.038). A subgroup analysis by age revealed a difference in microbial eradication rates in children (two to 11 years of age) that was statistically significant in favor of 0.5% levofloxacin. Microbial eradication was achieved in 87% of children treated with 0.5% levofloxacin, compared to 61.5% of children treated with 0.3% ofloxacin (P=0.032). There were no significant differences in microbial eradication rates between treatment groups for any of the other age subgroups. Clinical cure rates were similar between the 0.5% levofloxacin and 0.3% ofloxacin treatment groups at all time points assessed. At end point, 76% of patients in each treatment group were considered to be clinically cured. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days 3 through 5				No significant differences were noted between the treatment groups in resolution of baseline ocular signs at either the final visit or end point. In the 0.5% levofloxacin treatment group, 94% of patients had a resolution of photophobia compared to 73% of patients in the 0.3% ofloxacin treatment group (P=0.006). There were no significant differences between treatment groups in the overall incidence of adverse events. The most frequently reported non-ocular adverse event was headache (3%). The most common ocular adverse events were conjunctivitis in the non-study eye or worsening conjunctivitis in the infected eye (8%), burning (2%), eye pain (2%), and decrease in visual acuity (2%). Treatment-related adverse events were reported by 7.3 and 4.9% of patients receiving treatment with 0.5% levofloxacin and 0.3% ofloxacin, respectively. There were no significant differences between treatment groups in the incidence of treatment related adverse events. All treatment-related non-ocular adverse events were mild in severity. There were no notable differences between treatment groups for best-corrected visual acuity results or ophthalmoscopic findings over the course of the study. At end point, there was a statistically significant difference between treatment groups favoring 0.5% levofloxacin in the proportion of patients experiencing a change from baseline in palpebral conjunctival injection (P=0.009). There were no other significant differences between treatments in mean changes from baseline in biomicroscopy variables groups during the study. Ocular symptoms resolved more often in patients treated with 0.5% levofloxacin compared to patients treated with 0.3% ofloxacin. At end point, 64% of patients in the 0.5% levofloxacin treatment group experienced resolution of burning/stinging compared to 58% of patients in the 0.3% ofloxacin treatment group (P=0.025). Burning/stinging worsened in more patients treated with 0.3% ofloxacin (5%) compared to patients treated with 0.5% levofloxacin (1%). The mean changes from baseline in burning/stinging scores were -0.93 for 0.5% levofloxacin and -0.89 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.3% ofloxacin. There were no other notable differences between treatment groups for the safety evaluation of ocular symptoms during the study. When safety variable composite scores were analyzed to determine the number of patients who experienced a worsening from baseline at end point, significantly more patients in the 0.3% ofloxacin treatment group demonstrated a worsening of biomicroscopy results than in the 0.5% levofloxacin treatment group (8.2 vs 2%; P<0.05).
Tuber et al.[71] (2010) Moxifloxacin ophthalmic solution (Moxeza®) BID for 3 days vs placebo	DB, MC, PG, RCT, VC Patients ≥28 days of age with a diagnosis of bacterial conjunctivitis in one or both eyes based on bulbar conjunctival injection and discharge (score ≥1 on a four-point scale for each sign) and matting	N=1,180 6 days	Primary: Clinical cure rate and eradication rates by species Secondary: Not reported	Primary: Patients treated with moxifloxacin BID for three days had a microbiological success rate of 74.5% compared to 56.0% of patients treated with vehicle (P<0.0001). Moxifloxacin administered BID was significantly more effective than vehicle in eradicating the three principle conjunctivitis pathogens, *H influenzae* (98.5 vs 59.6%; P<0.001), *S pneumoniae* (86.4 vs 50.0%; *P*<0.001) and *S aureus* (94.1 vs 80.0%; P<0.001). Secondary: Not reported
Silver et al.[72] (2005) Moxifloxacin 0.5% ophthalmic solution 1 drop TID for 4 days vs ofloxacin 0.3% ophthalmic solution	MA Patients of any race with a diagnosis of bacterial conjunctivitis	N=1,978 7 to 9 days	Primary: Safety Secondary: Not reported	Primary: The most frequent adverse events experienced by all patients were ocular discomfort and transient burning and stinging, which were reported in more patients in the moxifloxacin group compared to the placebo group (2.8 vs 2.1%; P value not reported). In pediatric patients, similar results were found with ocular discomfort, transient burning and stinging reported as the most frequent adverse events experienced; these adverse events were reported in fewer patients in the moxifloxacin group when compared to the placebo group (1.9 vs 2.2%; P value not reported). The most common systemic adverse event reported in pediatric patients was increased cough that occurred in more patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1 drop QID for 4 days vs CIPRO 0.3% ophthalmic solution 1 drop TID for 4 days vs placebo				the moxifloxacin group than the placebo group (3.2 vs 2.8%; P value not reported). Similar rates of adverse events were reported in a study comparing moxifloxacin to ofloxacin with regard to keratitis, corneal infiltrate and ocular hyperemia (P value not reported). In a study comparing moxifloxacin to CIPRO, adverse events were also similar between the two groups with regard to tearing, ocular hyperemia, rash and rhinitis (P value not reported). Secondary: Not reported
Granet et al.[73] (2008) Moxifloxacin 0.5% ophthalmic solution TID for 7 days vs POLY and trimethoprim ophthalmic solution QID for 7 days	DB, MC, RCT Patients ≥1 month and <18 years of age with bacterial conjunctivitis	N=56 (84 eyes) 7 days	Primary: Clinical cure (defined as complete resolution of all ocular signs and symptoms at the 48-hour visit), clinical improvement (defined as at least 1 unit lower for each of the three cardinal ocular signs [bulbar conjunctival injection, palpebral conjunctival injection, and conjunctival discharge] at the 48-hour visit), non-responder rates (defined as	Primary: *Culture-positive eyes* A significantly greater percentage of culture-positive eyes in the moxifloxacin group achieved clinical cure compared to eyes in the POLY and trimethoprim group (81 vs 44%, respectively; P=0.001). The non-responder rate was significantly different at the 48-hour visit between the two treatment groups (P=0.001). At the 24-hour visit, more eyes treated with moxifloxacin showed a combined clinical cure and improvement (77.8%) than eyes treated with POLY and trimethoprim (59.4%; P=0.1011). *Culture-positive and culture-negative eyes* An analysis of all eyes showed moxifloxacin to be more effective at 48 hours than POLY and trimethoprim (P=0.0001). Non-resolution was significantly different at the 48-hour visit between the two treatment groups (P=0.0001). Of the eyes treated with moxifloxacin, only 2.3% were reported as not responding by 48 hours compared to 19.5% in the POLY and trimethoprim group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			a patient who did not meet success criteria at the time point evaluated) microbiological success (defined as eradication of all pre-therapy pathogens at the 48-hour visit) Secondary: Not reported	A telephone interview on day seven found that the three main symptoms of bacterial conjunctivitis were absent in both eyes of all patients in the two treatment groups. No treatment-related adverse events were reported in this study. Secondary: Not reported
Kodjikian et al.[74] (abstract) (2010) Moxifloxacin vs ofloxacin vs levofloxacin	MA (5 RCTs) Patients with a clinical diagnosis of acute bacterial conjunctivitis in one or more eyes	N=not reported Duration not reported	Primary: Clinical efficacy and drop-out rates for all reasons including lack of efficacy Secondary: Not reported	Primary: Treatment with moxifloxacin was more likely to achieve a clinical cure (OR, 1.59; 95% CI, 1.21 to 2.04; P<0.001) and were less likely to experience a treatment failure compared to treatment with placebo (OR, 3.61; 95% CI, 2.30 to 5.65; P<0.001). Moxifloxacin treatment was associated with a lower risk of therapy discontinuation compared to treatment with placebo (OR, 2.22; 95% CI, 1.62 to 3.03; P<0.001). In comparison to ofloxacin, patients treated with moxifloxacin had fewer dropouts for reasons other than treatment failure (OR, 1.92; 95% CI, 1.28 to 2.89; P=0.02) and fewer dropouts for treatment failure (OR, 2.53; 95% CI, 1.41 to 4.56; P=0.002). Secondary: Not reported
Williams et al.[75] (2013) POLY and trimethoprim ophthalmic solution 1 drop QID for 7 days	RCT, SB Patients 1 to 18 years of age with acute conjunctivitis	N=114 7 days	Primary: Clinical cure rate Secondary: Not reported	Primary: At the four-to-six day follow-up visit, 72 and 77% of patients in the POLY and trimethoprim and moxifloxacin groups were considered clinically cured, defined as a complete resolution of all signs and symptoms of conjunctivitis (P=0.59). Treatment with POLY and trimethoprim was shown to be non-inferior to moxifloxacin with a non-inferiority margin of 20% (difference, -0.05; 90% CI, -0.20 to 0.11). At the seven-to-ten day follow-up visit, 96 and 95% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs moxifloxacin 0.5% ophthalmic solution 1 drop TID for 7 days				POLY and trimethoprim and moxifloxacin groups were considered clinically cured (P value not reported). Bacteriologist cure rate was 61% in the POLY and trimethoprim group and 79% in the moxifloxacin group (P=0.52). Secondary: Not reported
Genée et al.[76] (1982) POLY and trimethoprim administered 6 times daily for 10 days vs POLY, NEO, and gramicidin administered 6 times daily for 10 days	DB, RCT Patients between the age of 8 and 80 years with a presumptive diagnosis of bacterial conjunctivitis	N=48 12 to 15 days	Primary: Microbiological eradication and sign/symptoms of bacterial conjunctivitis Secondary: Not reported	Primary: Bacteria were eradicated in all except two of the patients receiving POLY, NEO, and gramicidin and in all patients receiving POLY and trimethoprim (in whom bacteria were cultured at baseline). There was no significant difference between POLY and trimethoprim and POLY, NEO, and gramicidin in reducing sign and symptom scores during the follow-up period. Photographic differences between the treatment groups did not achieve significance either prior to or following treatment. However, a significant difference (P<0.05) was detected between mean scores of photographs taken before and after treatment with POLY, NEO, and gramicidin and before and after treatment with POLY and trimethoprim. No patient reported adverse reactions from either antibacterial preparation. Secondary: Not reported
Lohr et al.[77] (1988) POLY and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours while awake for 10 days	DB, RCT Patients between the ages of 2 months and 22 years of age with bacterial conjunctivitis	N=158 10 days	Primary: Clinical and bacteriological responses Secondary: Not reported	Primary: At the first follow-up visit, clinical cure or improvement was seen in 92, 95, and 89% of the patients treated with POLY and trimethoprim, gentamicin, and sulfacetamide, respectively. At the final follow-up visit, the number of patients clinically cured, improved or failed was not statistically different for the three treatment groups (P>0.1). The overall bacteriologic response was not statistically different for the three treatment groups (83, 68, and 72% for POLY and trimethoprim,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gentamicin 0.3% ophthalmic solution administered every 3 hours while awake for 10 days vs sulfacetamide 10% ophthalmic solution administered every 3 hours while awake for 10 days				gentamicin, and sulfacetamide, respectively; P>0.1). Secondary: Not reported
Gibson et al.[78] (1983) POLY and trimethoprim 10,000 units-0.1% QID daily for 7 days vs POLY, NEO, and gramicidin 5000 units-1700 units-25 units/mL QID for 7 days vs chloramphenicol 5 mg/mL* QID daily for 7 days	DB, MC, RCT Patients between 1 and 70 years of age with presumptive bacterial conjunctivitis	N=272 10 to 14 days	Primary: Signs and symptoms of bacterial conjunctivitis Secondary: Not reported	Primary: There was no significant difference between POLY and trimethoprim and POLY, NEO, and gramicidin (P>0.05) in reducing overall initial scores by 100% (cure) and 90% (very good improvement). POLY and trimethoprim was significantly more effective than chloramphenicol (P=0.03) in reducing overall initial scores by 100% (cure) and 90% (very good improvement. Secondary: Not reported
Kernt et al.[79]	MC, PG, RCT, SB	N=276	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) TOBY 0.3% ophthalmic solution (enhanced viscosity) 1 drop BID for 7 days vs TOBY 0.3% ophthalmic solution 1 drop QID for 7 days	Male and female patients with a negative pregnancy test prior to study entry who agreed to use birth control throughout the study, ≥1 year of age with bacterial conjunctivitis based on clinical observation	12 days	Percentage of patients with sustained cure/ presumed bacterial eradication based on final clinical judgment at TOC visit Secondary: Lid erythema/ swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/ exudates, tearing and epithelial disease; microbiology; safety	At the TOC visit, no statistically significant differences were seen between TOBY BID and TOBY QID with regard to sustained cure/presumed eradication (98 vs 99%, respectively; P=0.604). Secondary: No statistically significant differences were seen between the two groups with regard to lid erythema/swelling, palpebral conjunctiva, bulbar conjunctiva, conjunctival discharge/exudates and tearing (P value not reported). Persistence of the original infecting organism was confirmed in two patients treated with TOBY BID and in six patients treated with TOBY QID (P value not reported). Adverse events reported were mild to moderate in severity and were reported in 5.8% of the total number of patients in both groups. The most frequent ocular adverse events in the TOBY BID group were ocular pruritus (1.5%), ocular hyperemia (1.5%) and tearing (1.5%). Only ocular pruritus (0.7%) was reported in the TOBY QID (P value not reported).
Eradication of Nasal Colonization with *S aureus*				
Mody et al.[80] (2003) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for up to 2 weeks vs placebo	DB, PC, RCT Residents of Veterans Affairs and community long-term facilities with *S aureus* colonization	N=127 6 months	Primary: Nosocomial *S aureus* infection, nasal carriage of *S aureus* Secondary: Not reported	Primary: By the end of the treatment period, 93% of patients randomized to receive mupirocin ointment were no longer colonized with *S aureus*, compared to 15% of patients in the placebo group (P<0.001). One month after study entry, 88% of the patients on mupirocin therapy and 13% of patients in the control group remained free of *S aureus* colonization (P<0.001). *S aureus* colonization did not differ between the two study groups at six months after study onset (P<0.4). There was no statistically significant difference in the incidence of *S aureus* infection between patients receiving placebo and those on mupirocin therapy (15 vs 5%; P<0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wertheim et al.[81] (2004) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	DB, MC, PC, RCT Adult patients ≥18 years old with *S aureus* colonization hospitalized in non-surgical departments	N=1,602 2 weeks	Primary: Incidence of nosocomial *S aureus* infection Secondary: Time to nosocomial *S aureus* infection, duration of hospitalization, in-hospital mortality	Primary: There was no significant difference in the overall incidence of nosocomial *S aureus* infections between the mupirocin group (1.9%) and the placebo group (2.4%; 95% CI, -1.5 to1.9). Secondary: The mupirocin and placebo groups did not significantly differ in hospital mortality (3.0 vs 2.8%, respectively; 95% CI, -1.9 to 1.5). The mupirocin and placebo groups did not significantly differ in duration of hospitalization, median of eight days in both groups. Mupirocin group exhibited a delay in onset of nosocomial *S aureus* infection from 12 to 25 days, compared to placebo (P>0.2).
Harbarth et al.[82] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs placebo	DB, PC, RCT Patients ≥16 years old with MRSA colonization admitted to the hospitals	N=98 30 days	Primary: Incidence of overall MRSA carriage eradication Secondary: Nasal MRSA carriage eradication, MRSA infection rate, development of mupirocin resistance	Primary: There was no statistically significant difference in the overall MRSA eradication rate between the mupirocin group (25%) and the placebo group (18%; RR, 1.39; 95% CI, 0.64 to 2.99; P=0.40). Secondary: The was no statistically significant difference in the nasal MRSA eradication rate between the mupirocin group (44%) and the placebo group (23%) (RR, 0.57; 95% CI, 0.31 to 1.04; P=0.06). There was no statistically significant difference in the incidence of MRSA infections between the two groups (1.48 vs 2.82 infections per 1,000 patient days, respectively; RR, 0.52; 95% CI, 0.14 to 2.02; P=0.53). There was an association between low-level mupirocin resistance at study entry and subsequent treatment failure in both study groups (P=0.003). High-level mupirocin resistance was not identified in the study groups.
Perl et al.[83] (2002)	DB, PC, RCT Adult patients	N=3,864 30 days	Primary: Nosocomial *S aureus* infection,	Primary: The rates of *S aureus* infection at surgical sites among patients receiving mupirocin ointment (2.3%) and placebo (2.4%) were similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for up to 5 days prior to operative procedure vs placebo	undergoing elective, nonemergency, cardiothoracic, general, oncologic, gynecologic, or neurologic surgical procedure, no *S aureus* infection within one month of study onset, no nasal or facial bone disruption		nasal carriage of *S aureus* Secondary: Not reported	Among patients colonized with *S aureus*, the risk for developing a nosocomial *S aureus* infection at any site was significantly lower in patients receiving mupirocin ointment (4%) as compared to the placebo group (7.7%; OR, 0.49; 95% CI, 0.25 to 0.92; P=0.02). Nasal carriage was eliminated in 83.4% of patients randomized to mupirocin ointment as compared to 27.4% of patients receiving placebo therapy (P=0.001). Patients receiving six or more doses of mupirocin exhibited a greater rate of *S aureus* elimination (93.3%) compared to patients getting three to five doses of mupirocin ointment (81.3). Secondary: Not reported
van Rijen et al.[84] (2008) Mupirocin calcium nasal ointment vs placebo, no treatment or alternative topical treatment	MA (9 RCTs) Studies of nasal carriers of *S aureus* that were using hospital services (either as inpatient or outpatient)	N=3,396 Variable duration	Primary: *S aureus* infection rate Secondary: Mortality, adverse events, infection rate caused by other microorganisms than *S aureus*	Primary: A pooled analysis of trials comparing mupirocin to placebo or no treatment demonstrated a significant reduction in *S aureus* infection rate associated with mupirocin (RR, 0.69; 95% CI, 0.47 to 1.00). A planned subgroup analysis of surgical trials demonstrated a significant reduction in the rate of nosocomial *S aureus* infection rate with mupirocin (RR, 0.55; 95% CI, 0.34 to 0.89); however, this effect disappeared if the analysis only included surgical site infections caused by *S aureus* (RR, 0.63; 95% CI, 0.38 to 1.04). There was no statistically significant difference in rates of *S. aureus* infection between mupirocin-treated patients and neomycin-treated patients. Secondary: There was no significant difference in mortality between treated and untreated carriers (RR, 0.91; 95% CI, 0.64 to 1.31). No serious adverse events were observed or reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The infection rate caused by microorganisms other than *S aureus* was significantly higher in patients treated with mupirocin compared to control patients (RR, 1.38; 95% CI, 1.118 to 1.72).
Soto et al.[85] (1999) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days vs BAC ointment, 0.5 cm applied to each nostril TID for 5 days	RCT Healthcare workers colonized with *S aureus*	N=35 30 days	Primary: Rate of *S. aureus* eradication at 72-96 hours, and 30 days post topical antibiotic administration Secondary: Not reported	Primary: Nasal carriage was eradicated in 44% of patients randomized to BAC ointment as compared to 94% of patients receiving mupirocin therapy, as assessed 72 to 96 hours after administration of the topical antibiotic (P<0.01). Nasal carriage remained eradicated 30 days after study onset in 23% of patients randomized to BAC ointment as compared to 80% of patients receiving mupirocin therapy (P<0.01). Mild side effects occurred in 31% of patients in each of the two study groups and included itching, rhinitis, burning, congestion, unpleasant taste, and headache. Secondary: Not reported
Sit et al.[86] (2007) Mupirocin calcium nasal ointment 2%, applied to each anterior nostril BID for 5 days every 4 weeks vs no treatment	RCT Patients undergoing continuous ambulatory peritoneal dialysis for at least six months	N=49 1 year	Primary: Eradication of *S aureus* nasal carriage, incidence of peritonitis, exit site infection rates Secondary: Not reported	Primary: At the beginning of the study, the frequency of *S aureus* nasal carriage was similar in the two groups (47.9% in the mupirocin group, 50% in the control group). By the end of the study, *S aureus* had been eradicated in 13 of 23 (56.5%) patients in the mupirocin group, and 7 of 24 patients (29%) in the control group remained free of *S aureus*, as detected on nasal smear culture. By study completion, *S aureus* was not cultured from the nasal smear in patients in the mupirocin group, but in the control group, it was cultured at a rate of 20.8%. Peritonitis occurred at rates of 4.3% in the mupirocin group and 4.1% in the control group (P>0.05). In both groups, the same species of *Staphylococcus* was detected upon culture of the nasal smear and dialysate. No exit site infections were reported in either group during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Loeb et al.[87] (2003) Topical regimens (antibiotic or antiseptic ointments, antiseptic detergents) vs systemic antimicrobial agents vs placebo Results in this table are specific to mupirocin therapy.	MA (6 RCTs) Patients with nasal or extra-nasal MRSA colonization	N=384 Up to 6 months	Primary: MRSA eradication from all sites and incidence of MRSA infections Secondary: Not reported	Primary: *Mupirocin vs placebo* No significant difference was demonstrated in eradication of MRSA from all sites between the two groups on day 26 (RR, 1.39; 95%, CI 0.64 to 2.99). No evidence of a difference was demonstrated in eradication of MRSA from nasal sites alone on day 26 (RR, 1.77; 95% CI, 0.96 to 3.26). Ten MRSA infections occurred in this study, 3 of 46 in the mupirocin group and 7 of 50 in the placebo group (RR, 0.47; 95% CI, 0.13 to 1.70). *Mupirocin vs topical fusidic acid and oral trimethoprim-sulfamethoxazole* There was no significant difference in nasal eradication of MRSA between the two groups at 14 days (RR, 1.04; 95% CI, 0.93 to 1.15), 21 days (RR, 1.09; 95% CI, 0.97 to 1.23), 28 days (RR, 1.01; 95% CI, 0.88 to 1.16), and 90 days (RR, 1.10; 95% CI, 0.64 to 1.89). The investigators report that no evidence of differences in participants with extra-nasal eradication of MRSA was detected between the mupirocin and fusidic acid/trimethoprim-sulfamethoxazole groups at days 14 (83 and 76% eradication) and 28 (45 and 69%, respectively). Secondary: Not reported
van Rijen et al.[88] (2008) Mupirocin nasal ointment administered before surgery vs placebo or no treatment	MA (4 RCTs) Mupirocin-treated surgical patients with *S aureus* nasal carriage	N=1,372 5 days	Primary: Post-operative *S aureus* infection rate Secondary: Not reported	Primary: *Eradication of carriage* Perl et al. showed that nasal carriage of *S aureus* was eliminated in 83% of patients who received mupirocin, as compared to 27% of patients who received placebo (P<0.05). Kalmeijer et al. demonstrated that eradication occurred in 82% of patients who were initially carrying *S aureus* in the mupirocin group and in 29% of patients in the placebo group (P<0.05). Konvalinka et al demonstrated that nasal carriage was eliminated in 81.5% of patients receiving mupirocin and 46.5% of patients receiving placebo (P<0.0001). *Post-operative S aureus infection rate* Perl et al. showed a significant effect of mupirocin on the rate of *S. aureus*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				infection following surgery. Garcia et al., Kalmeijer et al., and Konvalinka et al. found no significant difference with mupirocin. Analysis of these four studies together showed a significant effect of mupirocin on the *S aureus* infection rate after surgery in carriers (RR, 0.55; 95% CI, 0.34 to 0.89). Secondary: Not reported
Ammerlaan et al.[89] (2009) Topically applied antibiotics (mupirocin nasal ointment, BAC nasal ointment, tea tree oil) vs oral antibiotics (tetracyclines, fusidic acid, macrolides, ciprofloxacin, rifampin, and trimethoprim-sulfamethoxazole) vs topical and oral antibiotic combination therapy	MA (23 RCTs) MRSA carriage in healthy individuals, health care workers, hospitalized patients and patients visiting outpatient clinics, and nursing home patients	N=2,114 Variable duration	Primary: Eradication of *S aureus* carriage Secondary: Not reported	Primary: *Topical treatments* The efficacy of mupirocin was comparable among studies that included only MSSA carriers or included both MRSA and MSSA carriers, and efficacy was also comparable among studies that included patients or healthy patients. The estimated pooled RR of treatment failure with mupirocin was 0.10 (range, 0.07 to 0.14). Mupirocin eradicates MRSA and MSSA carriage 11 times more effectively than no treatment, with successful eradication in 94% of carriers one week after treatment. The effects of mupirocin, compared to placebo, appeared to be effective on carriage at the end of follow-up, with estimated pooled RRs of treatment failure of 0.44 (range, 0.39 to 0.50). Eradication had been successful in 65% (range, 25 to 90%) of carriers after a follow-up period of at least 14 days. Overall, the efficacy of mupirocin was comparable among studies that included only MSSA carriers and studies that included both MRSA and MSSA carriers with pooled RRs at the end of follow-up of 0.52 (range, 0.43 to 0.64) and 0.40 (range, 0.34 to 0.48, respectively. Efficacy of mupirocin nasal ointment appeared to be lower in studies that included multiple body sites for evaluation (pooled RRs, 0.60; range, 0.49 to 0.74) compared to studies that only tested for nasal carriage (pooled RRs, 0.38; range, 0.32 to 0.45). BAC nasal ointment only eradicated carriage in 29% of MRSA and MSSA carriers at one week after treatment (range, 13 to 44%), and tea tree oil eliminated MRSA carriage in 44% of carriers at two weeks after treatment. Compared to mupirocin, estimated pooled RRs of treatment failure of BAC and tea tree oil at the end of treatment was 1.88 (range, 0.57 to 6.15).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Systemic treatments The overall pooled RRs of treatment failure of oral antibiotics, compared to placebo or no treatment, was 0.47 (range, 0.39 to 0.57) one week after treatment and 0.54 (range, 0.33 to 0.87) at the end of the follow-up period. Efficacies at the end of the follow-up period appeared to be comparable in studies that included only MSSA carriers or only MRSA carriers. In contrast with the results of mupirocin studies, the efficacy of systemic treatment, when compared to that of placebo or no treatment, was not higher in studies that determined eradication by means of nasal cultures only (pooled RRs, 0.74; range, 0.65 to 0.85), compared to those using cultures samples from multiple body sites (pooled RR, 0.40; range, 0.11 to 0.42). Trimethoprim-sulfamethoxazole in combination with rifampin or nasal fusidic acid eradicated MRSA carriage in 62% patients. Of the macrolides, monotherapy with clarithromycin reduced nasal MSSA carriage in 88% of patients at the end of eight weeks of follow-up, but it was also associated with a rapid and prolonged increase in macrolide resistance in oropharyngeal nonstaphylococcal flora. Combined treatment with DOXY, rifampin, mupirocin, and chlorhexidine was associated with MRSA eradication in 74% of patients after three months. Rifampin as part of combination therapy with other oral and/or topical antibiotics was associated with eradication of MRSA in 62% of carriers. Secondary: Not reported
Keratitis				
Leibowitz et al.[90] (1991) Ciprofloxacin 0.3% ophthalmic solution administered every 15 minutes for the first 6 hours, followed by every	MC, OL, PRO Patients with a presumed bacterial corneal ulcer	N=210 14 days	Primary: Physician's overall clinical impression of efficacy and clinical resolution of symptoms and signs Secondary:	Primary: Clinical success was achieved in 91.9% of patients treated with ciprofloxacin. There was no significant difference in the rate of clinical success among patients with mild, moderate and severe bacterial keratitis. Twelve (8.1%) of patients did not respond to ciprofloxacin and were considered treatment failures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
30 minutes for the remainder of day 0, followed by every hour on day 1, followed by every 4 hours on days 2 to 14			Not reported	There was a progressive resolution of symptoms and sings with ciprofloxacin over the course of the study. No serious adverse events were associated with the use of ciprofloxacin. Secondary: Not reported
Parmar et al.[91] (2006) Gatifloxacin 0.3% ophthalmic solution, frequency not reported vs ciprofloxacin 0.3% ophthalmic solution, frequency not reported	DB, RCT Patients with a diagnosis of bacterial keratitis	N=104 (104 eyes) Duration not specified	Primary: Healing of ulcers and microbiological outcomes Secondary: Not reported	Primary: Of the 41 eyes in the gatifloxacin group in which a complete follow-up was possible, 39 eyes (95.1%) exhibited a good response to treatment with complete healing of ulcer as compared to 38/47 eyes (80.9%) in the ciprofloxacin group (P=0.042). There was one severe ulcer with complete follow-up in each group. The severe ulcer treated with gatifloxacin healed completely, whereas the ulcer treated with ciprofloxacin failed to heal and ultimately required evisceration. The numbers were too small to analyze statistically. There was no significant difference in nonsevere ulcer healing rates with gatifloxacin or ciprofloxacin (95 vs 82.6%, respectively; P=0.08). Among the larger nonsevere ulcers (4 to 6 mm in size), there was no significant difference in the proportion of ulcers healing in the gatifloxacin group compared to the ciprofloxacin group (93.3 vs 77.4%, respectively; P=0.08). There was no significant difference in the number of smaller nonsevere ulcers (2 to 4 mm in size) that healed in the gatifloxacin group compared to the ciprofloxacin group (100 vs 93.3%, respectively; P=0.40). Considering culture-positive eyes alone, there was no significant difference between gatifloxacin and ciprofloxacin in the number of eyes that healed (92.9 vs 78.8%, respectively; P=0.165). The mean time to healing of ulcer in the gatifloxacin group was 13.9 days which did not differ significantly from that in the ciprofloxacin group (16. 8 days; P=0.43). The number of ulcers caused by gram-positive cocci that healed in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				gatifloxacin group were significantly higher than in the ciprofloxacin group (P=0.009). When considering individual pathogens, keratitis caused by *Staphylococcus epidermidis* (P=0.043) and by *Streptococcus pneumoniae* (P=0.007) showed a significantly better response to gatifloxacin than to ciprofloxacin. However, gram-positive bacilli and gram-negative organisms showed a similar sensitivity pattern to gatifloxacin and ciprofloxacin, and the percentages of ulcers caused by these organisms that healed in the gatifloxacin and ciprofloxacin groups did not differ significantly. Secondary: Not reported
Prajna et al.[92] (2001) Ofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, followed by every hour on days 2 to 4, followed by every 2 hours on days 5 to 21 vs ciprofloxacin 0.3% ophthalmic solution administered every 30 minutes on day 1, followed by every hour on days 2 to 4, followed by every 2 hours on days 5 to 21	DB, PG, RCT Patients with a microbiologic diagnosis of bacterial keratitis	N=217 3 weeks	Primary: Time to healing and reepithelialization accompanied by no progression of infiltration Secondary: Biomicroscopic findings, microbiologic findings on organism susceptibility and resistance, and patient reported symptoms	Primary: No significant differences were observed between the ofloxacin and ciprofloxacin treatment groups with regard to ulcer healing (85 vs 77%, respectively; P=0.32). Improvement in healing rates was observed in 6% of ofloxacin-treated patients and 10% of ciprofloxacin-treated patients; although the endpoint of total healing was not achieved in these patients. The average time to corneal healing was comparable in patients treated with either ofloxacin or ciprofloxacin, 13.7±0.7 and 14.4±0.8 days, respectively (P=0.80). Within seven days of treatment initiation, one third of the patients in each treatment group exhibited keratitis healing. By day 26 of treatment, 85% of the ofloxacin-treated patients and 77% of the ciprofloxacin-treated patients exhibited keratitis healing (P=0.32). Secondary: Treatment was discontinued prematurely in six patients in each treatment group because of perforation and in nine patients in each treatment group because of an insufficient therapeutic response. Ulcers that perforated had a significantly larger mean epithelial defect at baseline compared to those that healed (P=0.003). The stromal infiltration was also significantly larger in those patients who experienced perforation compared to those who did

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not (P=0.002). The etiologic pathogens were similar between those patients who experienced perforation and those who were discontinued from treatment prematurely because of an insufficient therapeutic response. No patient was discontinued from the study because of an adverse event. The most frequently reported events were burning and stinging after instillation of either study medication.
Miscellaneous Ocular Evaluations				
Bloom et al.[93] (1994) Ciprofloxacin 0.3% ophthalmic solution administered every 2 hours on days 0 to 1, followed by every 4 hours on days 2 to 6 vs TOBY 0.3% ophthalmic solution administered every 2 hours on days 0 to 1, followed by every 4 hours on days 2 to 6	DB, MC, RCT Patients with blepharitis or blepharo-conjunctivitis	N=464 7 days	Primary: Efficacy, signs and symptoms, physicians' impression of efficacy Secondary: Not reported	Primary: There were no significant differences in the treatment groups with regards to bacterial eradication, reduction, persistence, or proliferation after seven days of treatment. The majority of cases of blepharoconjunctivitis organisms were eradicated by treatment and blepharitis was either reduced or eradicated. Over the seven day period, significant reductions in scores for clinically apparent symptoms and signs were observed in both ciprofloxacin and TOBY treated groups. There were no significant differences between the two treatments (P<0.05). The physicians' overall impression of efficacy after seven days of treatment were as follows: improved or cured was noted in 82% of ciprofloxacin-treated patients and 84% of TOBY-treated patients; unchanged was noted in 18% (ciprofloxacin) and 15% (TOBY) of patients; worse was noted in one TOBY treated case (1 %) and no ciprofloxacin-treated cases. There were no significant differences between the two treatments. Ciprofloxacin was discontinued in one patient (0.4%) because of ocular discomfort. Treatment was discontinued in 3.5% of TOBY-treated patients. Adverse events led to the discontinuation of TOBY in a significantly higher proportion of cases than of ciprofloxacin (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kanda et al.[94] (2012) Levofloxacin 0.5% ophthalmic solution	MC, RETRO Patients who received ophthalmic levofloxacin for blepharitis, dacryocystitis, hordeolum, conjunctivitis, tarsadenitis, keratitis and/or corneal ulcer	N=6,686 (safety) N=5,929 (efficacy) Median 29 days for dacryo-cystitis; 8 to 9 days for all other infections	Primary: Adverse events, clinical response Secondary: Not reported	Primary: Forty-six adverse events were reported in 42 patients, with an overall incidence of 0.63%. The most commonly reported adverse events were ocular disorders such as blepharitis (0.1%), eye irritation (0.09%) and punctuate keratitis (0.07%). None of the reported adverse events were considered serious. A clinical response was observed in 95.5% of the 5,929 patients. Patients who were treated for dacryocystitis had a significantly lower response rate (88.3%) compared to patients treated for other diagnoses (overall, 95.8%; P<0.001). Secondary: Not reported
Gwon[95] (1992) Ofloxacin 0.3% ophthalmic solution administered 6 times daily on days 1 to 2, followed by QID on days 3 to 10 vs gentamicin 0.3% ophthalmic solution administered 6 times daily on days 1 to 2, followed by QID on days 3 to 10	DB, RCT Patients with suspected external ocular bacterial infection, including conjunctivitis, blepharitis, and blepharo-conjunctivitis	N=191 11 days	Primary: Cure or clinical improvement, signs and symptoms, microbiological improvement, adverse events Secondary: Not reported	Primary: Among patients treated with ofloxacin, 98% were either clinically cured or improved by day 11, compared to 92% of the gentamicin group. There were no significant differences between the groups in any of the improvement rates (P=0.089). The signs and symptoms of infection were judged to be completely resolved in 52% of the ofloxacin group compared to 44% of the gentamicin group at day 11. There were no differences in clinical improvement rates between patients with different baseline diagnoses. Ninety-eight percent of ofloxacin-treated patients with conjunctivitis were found to have improved by day 11, compared to 100% of those with other diagnoses. Among the gentamicin group, 91% and 100% of the patients with conjunctivitis and other diagnoses, respectively, had improved by day 11. None of the differences between the groups showed statistical significance. Microbiological improvement was achieved in 78% of the ofloxacin patients compared to 67% of the gentamicin group. There was no significant difference between the treatment groups. Ofloxacin treatment eradicated the infecting bacteria in 67% of patients at day 11, compared to 58% after gentamicin treatment. Proliferation occurred in 16% of the ofloxacin group vs 27% of gentamicin-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Among the ofloxacin patients, 78% improved overall (both clinically and microbiologically) compared to 63% of gentamicin patients. The observed differences in clinical, microbiological, or overall improvement rates between the ofloxacin and gentamicin groups were not statistically significant. Adverse reactions were reported by in 3.2% of ofloxacin patients and 7.1% of gentamicin patients. Secondary: Not reported
Gwon[96] (1992) Ofloxacin 0.3% ophthalmic solution 1 drop every 2 to 4 hours on days 1 and 2, followed by QID on days 3 through 10 vs TOBY 0.3% ophthalmic solution 1 drop every 2 to 4 hours on days 1 and 2, followed by QID on days 3 through 10	DB, MC, RCT Patients with the presence of conjunctival hyperemia, either eyelid crusting or discharge and positive bacterial culture	N=345 11 days	Primary: Clinical, microbiological and overall improvement rates Secondary: Change in cumulative summary score of 10 key biomicroscopic and symptomatologic variables and safety	Primary: Ofloxacin was found to have higher rates of microbiological (85.2 vs 77.6%) and overall (84.0 vs 77.6%) improvement rates when compared to TOBY at day 11, while TOBY was shown to have a higher clinical improvement rate (98.9 vs 100%); however, none of these differences were statistically significant (P=0.089 for all outcomes). Secondary: The decrease in cumulative summary score was found to be significantly greater in the ofloxacin group when compared to the TOBY group at visits on days three to five (P<0.050). Adverse reactions occurred more frequently in the TOBY group; however, this difference was not significant (0.6 vs 2.9%, respectively; P value not reported).
Foulks et al.[97] (1988) POLY and trimethoprim 10,000 units-0.1%	DB, RCT Patients ≥2 months of age with bacterial ocular surface infections	N=39 3 to 6 days	Primary: Clinical improvement, cure rates, microbiological cure rates	Primary: Clinical improvement was similar in both treatment arms (POLY and trimethoprim, 20%; POLY, trimethoprim, and sulfacetamide, 29%) as were the cure rates (POLY and trimethoprim, 80%; POLY, trimethoprim, and sulfacetamide, 71%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ophthalmic solution administered every 3 hours for 10 days vs POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days	(conjunctivitis, blepharitis or blepharo-conjunctivitis)		Secondary: Not reported	Microbiologic cure rates were similar among the treatment groups with POLY and trimethoprim showing a pathogen eradication rate of 87% and POLY, trimethoprim, and sulfacetamide an eradication rate of 93%. Differences in clinical and microbiologic responses were not statistically significant. Adverse events were similar between the treatment groups. Secondary: Not reported
Lamberts et al.[98] (1984) <u>Study 1</u> POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs NEO, POLY, and gramicidin 2.5 mg-5,000 units-0.025 mg/mL ophthalmic solution administered every 3 hours for 10 days	DB, RCT Patients ≥2 months of age with conjunctivitis, blepharitis, or blepharo-conjunctivitis	N=68 17 days	Primary: Cure or clinical improvement, microbiological cure, adverse events Secondary: Not reported	Primary: *Study 1* Clinical cure or improvement was observed in 95% of patients receiving Solution 1 compared to 72% of patients receiving Solution 2. There was no significant difference between the treatment groups. The numbers of microbiologic cures for Solutions 1 and 2 were 82% and 90%, respectively. There was no significant difference between the treatment groups. Of the 35 patients treated with Solution 2, three had adverse reactions and left the study. Of the 33 patients using Solution 1, four had reactions of similar severity. There was no significant difference between the treatment groups. *Study 2* Clinical cure or improvement was observed in 82% of patients receiving Solution 1 compared to 77% of patients receiving Solution 3. There was no significant difference between the treatment groups. The numbers of microbiologic cures for Solutions 1 and 3 were 62% and 85%, respectively. There was no significant difference between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Solution 2) <u>Study 2</u> POLY, trimethoprim, and sulfacetamide 10,000 units-0.1%-0.5% ophthalmic solution administered every 3 hours for 10 days (Solution 1) vs POLY and trimethoprim 10,000 units-0.1% ophthalmic solution administered every 3 hours for 10 days (Solution 3)				Three of the patients using Solution 3 and two of the patients using Solution 1 had adverse reactions. There was no significant difference between the treatment groups. Secondary: Not reported
Laibson et al.[99] (1981) TOBY 0.3% ophthalmic solution administered every 2 hours for 2 days, followed by every 4 hours for 8 days vs gentamicin 0.3% ophthalmic solution administered every 2	DB, RCT Patients with acute superficial ocular inflammations of presumed bacterial origin	N=66 10 days	Primary: Cure or clinical improvement Secondary: Not reported	Primary: The cure and improvement frequencies of the two drugs were similar, 93% for TOBY and 92% for gentamicin sulfate. The differences in degree of improvement obtained with the two antibiotics were not statistically significant. Four of 28 patients (14.3%) treated with gentamicin sulfate and three of 38 patients (7.9%) treated with TOBY had adverse reactions. The difference was not statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours for 2 days, followed by every 4 hours for 8 days				
Leibowitz et al.[100] (1981) TOBY 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10 vs gentamicin 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10	DB, RCT Patients with superficial bacterial infections	N=93 10 days	Primary: Clinical response, physicians' judgment of clinical response to therapy, antibacterial efficacy, adverse reactions Secondary: Not reported	Primary: Patients in both treatment groups had similar reduction in sign and symptom scores following 10 days of treatment. There was no significant difference between the treatment groups. Based on the physician's judgment of response to therapy, 97% of the TOBY-treated patients were judged to be cured or better vs 91% of gentamicin-treated patients. There was no significant difference between the treatment groups. Results of the antibacterial efficacy of the two treatments at the lid margin were similar (P>0.05). Among the TOBY-treated patients, 9.3% experienced adverse reactions compared to 17.6% of patients in the gentamicin treatment group. Secondary: Not reported
Cagle et al.[101] (1981) TOBY 0.3% ophthalmic solution administered every 2 hours on days 1 to 2, followed by QID on days 3 to 10 vs TOBY 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3,	DB, MC, RCT Patients with acute bacterial infections with ocular inflammation, including conjunctivitis, blepharitis, blepharo-conjunctivitis and blepharokerato-conjunctivitis	N=511 11 days	Primary: Cure or clinical improvement, microbiological improvement, adverse events Secondary: Not reported	Primary: There were no significant differences in efficacy between the gentamicin solution and ointment formulations or between the TOBY solution and ointment formulations. TOBY (combined data for both formulations) was clinically more effective than gentamicin (combined data for both formulations) when evaluating the number of patients that were cured, improved, or unimproved (P=0.038). However, there was no significant difference between TOBY and gentamicin when the two solutions or ointments were compared separately. TOBY solution and ointment eradicated or controlled 91.4% of the invasive bacteria on the conjunctiva compared to 84.2% with gentamicin treatment (P=0.011). There was no significant difference between the treatment groups when evaluating the antibacterial effect of TOBY and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by TID on days 4 to 10 vs gentamicin 0.3% ophthalmic solution administered every 2 hours on days 1 to 2, followed by QID on days 3 to 10 vs gentamicin 0.3% ophthalmic ointment administered 5 times daily on days 1 to 3, followed by TID on days 4 to 10				gentamicin on the skin-lash margin (P=0.879). When comparing one ointment vs the other, or the two solutions, the results were not statistically different. Adverse events occurred in 10.6% of patients receiving gentamicin ointment and 3.7% of patients receiving TOBY ointment (P=0.017). Secondary: Not reported
Otitis Externa				
Drehobl et al.[102] (2008) Ciprofloxacin 0.2% otic solution BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic solution TID for 7 days	MC, PG, RCT Patients ≥2 years of age with acute diffuse otitis externa of less than 3 weeks' duration	N=630 15 to 17 days	Primary: Clinical cure of otitis symptoms at the TOC visit Secondary: Clinical cure at the EOT visit, percentage of patients with clinical improvement, resolution and/or improvement of otalgia at EOT and TOC visits,	Primary: The percentage of patients with clinical cure at the TOC visit in the clinical intent-to-treat population was 81.4% in the ciprofloxacin group and 76.7% in the NEO, POLY, and HYDRO group. In the clinical per-protocol population, clinical cure at the TOC visit was 86.6% in the ciprofloxacin group and 81.1% in the NEO, POLY, and HYDRO group. There were no significant differences between the treatment groups for either outcome. Secondary: The percentage of patients with clinical cure at the EOT visit was 70.0% in the ciprofloxacin group and 60.5% in the NEO, POLY, and HYDRO group. There was no significant difference between the treatment groups. Clinical improvement at the EOT visit was reported in 92.7% of patients in ciprofloxacin group compared to 88.5% in the NEO, POLY, and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	HYDRO group. At the TOC visit, clinical improvement was similar in the ciprofloxacin group (89.5%) and the NEO, POLY, and HYDRO group (83.1%). Patients treated with ciprofloxacin and NEO, POLY, and HYDRO had similar percentages of resolution of otalgia at the EOT and TOC visits. The percentage of patients with clinical microbiologic cure in the EOT visit was 69.5% in the ciprofloxacin group compared to 59.8% in the NEO, POLY, and HYDRO group. At the TOC visit, the percentage of patients with clinical microbiologic cure increased to 85.1% in the ciprofloxacin group and 78.2% in the NEO, POLY, and HYDRO group. In both treatment groups, most treatment-emergent adverse events were of mild intensity and unrelated to the study medication. The incidence of treatment-related adverse events was 3.8 and 3.6% for ciprofloxacin and PNH, respectively.
Roland et al.[103] (2004) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	MC, PG, RCT Patients ≥1 year of age with a clinical diagnosis of mild, moderate, or severe AOE and intact tympanic membranes	N=468 18 days	Primary: Clinical cure rates at the day 18 (TOC) visit, microbiologic eradication rates at the day 18 (TOC) visit in patients with positive baseline ear cultures Secondary: Investigators' assessments of clinical responses and of individual signs and symptoms of AOE at each study visit	Primary: The clinical cure rate at the day 18 (TOC) visit was significantly higher with CIPRO and DEX than with NEO, POLY, and HYDRO (90.9 vs 83.9%; P=0.0375). The microbiologic eradication rate in the culture positive patient population was significantly higher with CIPRO and DEX treatment than with NEO, POLY, and HYDRO treatment at the day 18 (TOC) visit (94.7 vs 86.0%; P=0.0057). Secondary: The investigators' assessment of the clinical response at each study visit showed CIPRO and DEX to be significantly more effective than NEO, POLY, and HYDRO in achieving a clinical cure at the day three and day 18 visits (P=0.0279 and P=0.0321, respectively). The two treatments were equally effective at day eight. Analyses of the individual signs and symptoms of AOE showed that CIPRO and DEX treatment was significantly more effective in reducing inflammation than NEO, POLY, and HYDRO treatment at day 18

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.0268). Other signs and symptoms showed no significant differences between the two treatments at day 18. Adverse events reported during the study were generally mild-to-moderate and usually resolved with or without treatment. Otic adverse events considered therapy-related included pruritus in three patients (1.3%) receiving CIPRO and DEX and nine patients (3.8%) receiving NEO, POLY, and HYDRO.
Roland et al.[104] (2007) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	MC, PG, RCT Patients ≥1 year of age with a clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) AOE of <4 weeks duration in one or both ears and intact tympanic membranes	N=524 18 days	Primary: Patient assessment of ear pain and analgesic use; investigator-assessed inflammation, edema, tenderness, and discharge on study days three, eight, and 18 Secondary: Not reported	Primary: Patient-reported results revealed a greater percentage of CIPRO and DEX-treated patients experienced relief of severe pain across time (P=0.0013) and relief of significant pain (moderate or severe) across time (P=0.0456) compared to NEO, POLY, and HYDRO-treated patients. CIPRO and DEX-treated patients had significantly less pain than NEO, POLY, and HYDRO-treated patients on day two (P=0.0204) and day three (P=0.0364). Evaluation of analgesic use showed no difference between treatment groups in the percentage of patients who used no analgesics, nonnarcotic analgesics, or narcotic analgesics (P>0.05). Significantly less inflammation (P=0.0043) and edema (P=0.0148) were reported with CIPRO and DEX at the investigator assessment on day three. No difference in tenderness or discharge was observed between treatments. No differences were noted between treatments in terms of reported incidence or types of adverse events. No patients in either treatment group discontinued the study because of treatment-related adverse events. Secondary: Not reported
Rahman et al.[105] (2007) CIPRO and DEX 0.3-0.1% otic	Pooled analysis of 2 RCTs Patients ≥1 year of age diagnosed	N=1,072 18 days	Primary: Clinical cure rates and time to cure Secondary:	Primary: Following seven days of therapy, 98.1% of CIPRO and DEX-treated patients and 95.7% of NEO, POLY, HYDRO-treated patients were clinically cured.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
suspension BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	with AOE		Not reported	The mean time to cure was 9.7 days in the CIPRO and DEX group compared to 10.3 days in the NEO, POLY, HYDRO group. The proportion of patients cured at the day-three, -eight, and -18 assessments between the CIPRO and DEX and NEO, POLY, HYDRO treatment groups were 0.14 and 0.10; 0.75 and 0.72; and 0.98 and 0.97. Treatment-related adverse event rates were similar between the two groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%). Secondary: Not reported
Dohar et al.[106] (2009) CIPRO and DEX 0.3-0.1% otic suspension 3 to 4 drops BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension BID to TID for 7 days	Pooled analysis of 2 RCTs Patients >1 year of age with AOE and intact tympanic membranes who were positive for *P aeruginosa* and *S aureus* at baseline	N=789 18 days	Primary: Treatment failure rates, MIC_{50}, and MIC_{90} values for *P aeruginosa* and *S aureus* Secondary: Not reported	Primary: Treatment with CIPRO and DEX was associated with a significantly lower treatment failure rate against *P aeruginosa* (5.1%) than NEO, POLY, HYDRO (13.0%; P=0.0044). For *P aeruginosa*, the MIC_{50} values were lowest for CIPRO (0.13 mg/mL), followed by POLY (0.5 mg/mL), NEO (8 mg/mL), and POLY and NEO combined (1.0 and 3.2 mg/mL). MIC_{90} values of each antibiotic preparation were 2- to 4-fold higher than MIC_{50} except for POLY, which had identical MIC_{50} and MIC_{90} values. The overall treatment failure rates for *S aureus* were similar between CIPRO and DEX and NEO, POLY, HYDRO (7.3 vs 6.9%; P=0.9463). For *S aureus*, the CIPRO MIC_{50} was 0.25 mg/mL; the POLY MIC_{50} was 65 mg/mL, the NEO MIC_{50} was 0.5 mg/mL, and the POLY and NEO MIC_{50} was 0.25 and 0.80 mg/mL. MIC_{90} were 2- to 4-fold higher than MIC_{50} values. Secondary: Not reported
Pistorius et al.[107] (1999)	RCT	N=842	Primary: Clinical success	Primary: For the per-protocol population, clinical success at the end of therapy was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CIPRO 0.2% otic solution or CIPRO and HYDRO 0.2-1.0% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	Patients ≥2 years of age with acute diffuse bacterial otitis externa of less than 3 weeks' duration	14 to 28 days posttreatment	(resolution or improvement), bacteriological eradication, and adverse events Secondary: Not reported	reported in 93% of CIPRO-treated patients, 90% of CIPRO and HYDRO-treated patients, and 87% of NEO, POLY, and HYDRO-treated patients. CIPRO and CIPRO and HYDRO were found to be statistically equivalent to NEO, POLY, and HYDRO therapy (95% CI, -0.0 to 10.5 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, -3.3 to 8.0 for CIPRO and HYDRO vs NEO, POLY, and HYDRO). For the intent-to-treat population, the clinical response was also statistically equivalent between CIPRO or CIPRO and HYDRO and NEO, POLY, and HYDRO. At the end of therapy, clinical success was reported in 91%, 91%, and 89% of the intent-to-treat patients in the CIPRO, CIPRO and HYDRO, and NEO, POLY, and HYDRO treatment groups, respectively. At the follow-up evaluation, continued resolution was observed in 97% of CIPRO-, 98% of CIPRO and HYDRO-, and 95% of NEO, POLY, and HYDRO-treated patients. Estimated median time-to-end of ear pain in the population valid for efficacy was 4.7 days for the CIPRO group, 3.8 days for the CIPRO and DEX group, and 4.1 days for the NEO, POLY, and HYDRO group. Treatment with CIPRO and HYDRO resulted in a statistically significantly shorter time-to-end of ear pain when compared to CIPRO (P=0.039). The percentage of patients who took pain medications was similar across the treatment groups. Fifty percent of the CIPRO patients, 51% of the CIPRO and HYRDO patients, and 53% of the NEO, POLY, and HYDRO patients used analgesics for ear pain. The median time to a 50% reduction in ear pain was 2.47 days for CIPRO, 2.08 days for CIPRO and HYDRO, and 2.03 days for NEO, POLY, and HYDRO. Bacteriologic eradication at the end of therapy was 92% in the CIPRO-, 95% in the CIPRO and HYDRO-, and 87% in the NEO, POLY, and HYDRO-treatment groups (95% CI, -2.0 to 12.4 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, 0.3 to 13.7 for CIPRO and HYDRO vs NEO, POLY, and HYDRO).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At least one treatment- emergent event was reported in 23% of CIPRO-, 25% of CIPRO and HYDRO-, and 20% of NEO, POLY, and HYDRO-treated patients. Drug-related events were similar among the three treatment groups (6% CIPRO, 5% CIPRO and HYDRO, 5% NEO, POLY, and HYDRO). Headache, ear pain, and pruritus were the most common events reported in all three treatment groups. Most adverse events were mild to moderate in severity (94% CIPRO, 94% CIPRO and HYDRO, 95% NEO, POLY, and HYDRO) and improved or resolved with sufficient follow- up. Secondary: Not reported
Jones et al.[108] (1997) Ofloxacin 0.3% otic solution BID for 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic solution QID for 10 days	2 RCTs Adults (≥12 years of age) and children (≥1 and ≤11 years of age) with clinically diagnosed, unilateral or bilateral, stable or exacerbating otitis externa of 2 weeks' duration or less with purulent or mucopurulent otorrhea	N=314 17 to 20 days	Primary: Overall clinical efficacy in the clinically evaluable population Secondary: Not reported	Primary: The overall clinical response was cure in 97% of ofloxacin-treated children and 95% of NEO, POLY, and HYDRO-treated children (P=0.48). The overall clinical response was cure in 82% of ofloxacin-treated adults and 84% of NEO, POLY, and HYDRO-treated adults (P=0.56). The rates of success in the overall clinical and microbiological responses were also comparable between treatment groups in both populations. Ofloxacin and NEO, POLY, and HYDRO demonstrated comparable efficacy (≥98%) in eradicating all pathogens. Compliance in adults was comparable in both treatment groups (91% for ofloxacin-treated and 86% for NEO, POLY, and HYDRO-treated patients). Compliance in children was also comparable in both treatment groups (94% for ofloxacin-treated and 84% for NEO, POLY, and HYDRO-treated patients). No significant differences between treatment groups were observed with respect to subject or patient or guardian satisfaction at during-therapy and post-therapy visits. There were no significant differences in the incidence of any individual treatment related adverse event between treatment arms. The most common treatment-related adverse events reported in adults were pruritus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(6.3 and 3.8% of ofloxacin- and NEO, POLY, and HYDRO-treated adults, respectively) and application site reactions (3.8% in each treatment group). The most common treatment-related adverse events reported in children were application site disorders in 2.1% of NEO, POLY, and HYDRO-treated children and no ofloxacin-treated children. Secondary: Not reported
Schwartz et al.[109] (2006) Ofloxacin 0.3% otic suspension QD for 7 to 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension QID for 7 to 10 days	MC, PG, RCT Pediatric patients aged ≥6 months and ≤12 years with stable or exacerbating symptoms of otitis externa of less than 2 weeks' duration	N=278 17 to 20 days	Primary: Overall clinical response (defined as cure in the clinically evaluable patients demonstrated by resolution of otitis externa signs and symptoms at the test of cure visit) Secondary: Compliance, signs and symptoms, microbiological eradication, adverse events	Primary: The clinical response at the test of cure visit (seven to 10 days posttreatment) was cure (sustained clinical cure and subsequent clinical cure) in 96.5 and 95.8% of patients receiving ofloxacin otic solution and NEO, POLY, and HYDRO otic suspension, respectively (P=0.097). The clinical cure rates in the overall clinical response were equivalent between the treatment groups. The clinical cure rates were 93.8 and 94.7% in the ofloxacin-treated and NEO, POLY, and HYDRO-treated patients, respectively (P=0.763). The clinical response at the end of therapy visit (days 7-9) was cure in 77.9 and 64.2% of patients receiving ofloxacin otic solution and NEO, POLY, and HYDRO otic suspension, respectively (P=0.045). Secondary: Mean subject compliance (P<0.001) and mean overall percent patient compliance (P=0.008) were significantly higher in the ofloxacin otic solution group than in the NEO, POLY, and HYDRO group. The mean overall percent compliance for ofloxacin patients was 93.2 vs 84.1% for patients taking NEO, POLY, and HYDRO otic suspension (P<0.001). Mean scores for all signs and symptoms were similar between the two treatment groups. At the end of therapy visit, 69.6% (39/56) of the ofloxacin-treated patients and 67.6% (23/34) of the NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured. At the test of cure visit, 100.0% (54/54) of the ofloxacin-treated patients and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				97.0% (33/34) of the NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured (combined sustained clinical cure and subsequent clinical cure). Treatment-related adverse events were similar in both treatment groups and were mild to moderate in severity. The adverse events reported with highest frequency were application-site reaction (22.3 and 20.3% of the ofloxacin-treated and NEO, POLY, and HYDRO-treated patients, respectively) and earache (7.2 and 4.3% of the ofloxacin treated and NEO, POLY, and HYDRO-treated patients, respectively).
Rosenfeld et al.[110] (2006) Various topical antimicrobials with or without corticosteroids	MA (20 RCTs) Patients with diffuse AOE	N=3,289 Variable duration	Primary: Clinical cure rates (defined as absence of all presenting signs and symptoms of diffuse AOE) or improvement (defined as partial or complete relief of presenting signs and symptoms), bacteriological cure rates Secondary: Not reported	Primary: *Antimicrobial vs placebo* Topical antimicrobial increased absolute clinical cure rates of AOE by 46% and bacteriologic cure rates by 61% compared to placebo. The 95% CI for the clinical cure rate is consistent with a NNT of 1.5 to 3.5 patients. Treatment with topical NEO, colistin, and HYDRO was associated with less severe edema and itching at day three compared to placebo ($P<0.05$), and less severe edema, itching, redness, scaling, and weeping at day seven ($P<0.05$). *Antiseptic vs antibiotic* Topical antiseptic and topical antibiotic achieved comparable clinical cure rates at seven to 14 days. *Quinolone antibiotic vs non-quinolone antibiotic* Topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates at three to four days, seven to 10 days, and 14 to 28 days and comparable clinical improvement rates at seven to 10 days. Quinolones used in the meta-analyses were ofloxacin, CIPRO alone, or CIPRO combined with DEX or HYDRO. The antibiotic comparators used were gentamicin, TOBY, or POLY and HYDRO combined with NEO or oxytetracycline. None of the comparisons were statistically significant. Topical quinolone therapy increased absolute bacteriologic cure rates by 8.0% over non-quinolone antibiotic therapy. This result was highly influenced by one study with a small sample size. When this study is

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				excluded from the MA, the results were no longer statistically significant (P=0.079). Three studies that compared adverse events showed no overall combined difference between a quinolone preparation and NEO, POLY, and HYDRO. The most common events reported were pruritus (about 7%) and site reaction (5%); other events with an incidence less than 2% included rash, discomfort, otalgia, dizziness, vertigo, superinfection, and reduced hearing. *Antimicrobial/steroid vs antimicrobial alone* Topical antimicrobial/steroid and topic antimicrobial alone achieved comparable clinical and bacteriologic cure rates at seven days. Antimicrobial and steroid combinations used in the MAs were CIPRO and HYDRO, CIPRO and DEX, and acetic acid and triamcinolone. The antibiotic comparator in all studies was the same antimicrobial without the steroid. *Steroid/antibiotic vs steroid alone* Topical steroid alone increased absolute clinical cure rates by 20% at seven to 11 days compared to topical steroid and antibiotic combination therapy. Steroids used in the MAs were betamethasone and HYDRO butyrate. The antibiotic and steroid comparator was oxytetracycline, POLY, and HYDRO in both trials. Although the overall effect is statistically significant, the 95% CI is broad and the lower limit approaches zero (0.03). Similarly, the 95% CI for the NNT (five to 33 patients) cannot exclude a trivial effect. Secondary: Not reported
Otitis Media				
Mair et al.[111] (2016) Ciprofloxacin suspension 6% (Otiprio®)	Two identical DB, MC, PRO, sham-controlled, RCTs Patients 6 months to 17 years of age	N=532 29 days	Primary: Treatment failure at day 15, including the presence of otorrhea, use of	Primary: The primary end point of cumulative proportion of treatment failures at day 15 was 24.6% in trial 1 and 21.3% in trial 2 for patients in the ciprofloxacin groups compared with 44.8% in trial 1 and 45.5% in trial 2 for patients in the sham treatment groups (ORs for ciprofloxacin vs sham treatment, 0.39; 95% CI, 0.22 to 0.68; and 0.30; 95% CI, 0.17 to 0.53,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs Sham treatment	with bilateral middle ear effusion requiring tympanostomy tube placement		otic or systemic antibiotics, loss to follow-up, or missed visits Secondary: Safety	respectively; P<0.001 for both). Secondary: In both trials, no serious or life-threatening adverse events related to the study drug occurred, and no treatment-emergent adverse effects resulted in patient discontinuation from either trial. Most adverse events were mild or moderate in severity. The proportions of patients who experienced treatment-emergent adverse effects were 48.6% for trial 1 and 57.3% in trial 2 among the ciprofloxacin groups and 55.8% in trial 1 and 54.0% in trial 2 among the sham treatment groups. The most frequent treatment-emergent adverse effects for both groups were nasopharyngitis, irritability, and rhinorrhea.
Dohar et al.[112] (2018) Ciprofloxacin suspension 6% (Otiprio®)	MC, OL, PRO Patients aged 6 months to 17 years with a history of otitis media requiring bilateral tympanostomy tube placement	N=410 (per-protocol population) 8 weeks	Primary: Rates of otorrhea through weeks four and eight and the rate of otorrhea via unscheduled visits through Day 15 Secondary: Safety	Primary: In per-protocol population, otorrhea rates through Day 15 were 8.8% (95% CI, 5.7 to 12.8%), 6.6% (95% CI, 2.2 to 14.7%), 3.3% (95% CI, 0.4 to 11.3%) in wet/wet, wet/dry, and dry/dry ears, respectively. For Medicaid patients through Day 15, Week four and Week eight, otorrhea rates were 8.1% (95% CI, 4.1 to 14.1%), 17.0% (95% CI, 11.1 to 24.5%), and 17.8% (95% CI, 11.7 to 25.3%) compared with those non-Medicaid insured: 7.3% (95% CI, 4.5 to 11.0%), 14.5% (95% CI, 10.6 to 19.3%), and 21.8% (95% CI, 17.1 to 27.2%), respectively. Secondary: The most common adverse events related to study drug as assessed by the investigator were: device occlusion, ear pain and pyrexia. No patients had a treatment-emergent adverse event leading to study discontinuation, and no patients had a treatment-emergent adverse event leading to death.
Miro et al.[113] (2000) CIPRO 0.2% otic solution BID for 10 days vs NEO, POLY, and	MC, OL, RCT Patients 14 to 71 years of age with chronic suppurative otitis media (defined as serous, mucous, mucopurulent, or purulent	N=232 1 month following the end of therapy	Primary: Clinical response at visit two Secondary: Clinical response at visit 3 and bacteriologic outcome at visits two and three	Primary: In the per protocol population, 91% of patients in the CIPRO and 87% of patients in the NEO, POLY, and HYDRO group were cured at visit two (90% CI, -8.86 to 4.8; P value not significant). In the evaluable patients and the randomized patients, the percentages of patients classified as cured at visit two were 90% and 87%, respectively in the CIPRO group and 81% and 76%, respectively in the NEO, POLY, and HYDRO group (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HYDRO 3.5 mg-10,000 units-1% otic suspension QID for 10 days	otorrhea), a history of persistent tympanic perforation or the presence of a tympanostomy tube along with the current episode lasting for at least 6 weeks, and bacteriologic confirmation of ear infection			Secondary: At visit three (one month after the end of treatment), 78% of patients in both the CIPRO and NEO, POLY, and HYDRO groups had sustained cure and 5% of patients (4% in the CIPRO group and 6% in the NEO, POLY, and HYDRO group) showed a relapse of otorrhea. The rate of bacterial eradication was 79% in the CIPRO group and 76% in the NEO, POLY, and HYDRO group. The most frequently reported adverse events were pruritus, stinging, earache, passage of the medication into the mouth, vertigo, and cephalea.
Dohar et al.[114] (2006) CIPRO and DEX0.3-0.1% otic suspension 4 drops BID for 7 days vs amoxicillin and clavulanic acid 600-42.9 mg every 12 hours for 10 days	MC, PG, RCT Children 6 months to 12 years of age with AOM with otorrhea through tympanostomy tubes of ≤3 weeks' duration and visible otorrhea	N=80 18 days	Primary: Time to cessation of otorrhea and clinical cure at TOC Secondary: Microbiologic response	Primary: The median time to cessation of otorrhea for CIPRO and DEX was 4.0 days (ITT and modified ITT) compared to 7.0 days (ITT) and 9.5 days (modified ITT) for amoxicillin and clavulanic acid (ITT; P=0.006, modified ITT; P=0.0011). Clinical cure at TOC occurred in 84.6 and 80.7% of patients receiving CIPRO and DEX (ITT and modified ITT, respectively) compared to 58.5 and 55.2% of patients receiving amoxicillin and clavulanic acid (ITT and modified ITT, respectively; P=0.0100 and P=0.0340, respectively). Secondary: The difference in the microbiologic response between the two treatment groups in the modified per-protocol data set was not statistically significant (83 vs 63%).
Roland et al.[115] (2003) CIPRO and DEX 0.3-0.1% otic suspension 3 drops BID for 7 days vs	MC, PG, RCT Children 6 months to 12 years of age with AOM with tympanostomy tubes and otorrhea for ≤3 weeks' duration	N=201 17 days	Primary: Time to cessation of otorrhea Secondary: Physicians' assessment of the clinical	Primary: The mean time to cessation of otorrhea in the culture-positive population was 4.22 days in patients receiving CIPRO and DEX compared to 5.31 days in those receiving CIPRO alone (P=0.004). Secondary: Patients receiving CIPRO and DEX showed significantly improved clinical responses at the day three (P<0.0001) and day eight (P<0.0499) visits in comparison with those receiving CIPRO alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CIPRO 0.3% otic solution 3 drops BID for 7 days			response, reduction of granulation tissue, antimicrobial response	There were no statistically significant differences in reduction of granulation tissue between the two treatment groups at any visit. There were no significant differences between the two treatments in continued tympanostomy tube patency (97% in both groups). Of the 75 clinically and microbiologically evaluable patients in the CIPRO and DEX-treated group, 68 patients were microbiological successes, with all pretherapy pathogens eradicated. There were seven microbiological failures in this treatment group, giving an overall CIPRO and DEX success rate of 90.7%. Of the 64 evaluable patients in the CIPRO-treated group, 51 patients were microbiological successes, with all pretherapy pathogens eradicated. There were 14 microbiological failures in this treatment group, giving an overall CIPRO success rate of 79.7%. There was no significant difference between the treatment groups (P=0.0660).
Roland et al.[116] (2004) CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs ofloxacin 0.3% otic solution BID for 10 days	PG, RCT Children who were aged 6 months to 12 years and had patent tympanostomy tubes and a clinical diagnosis of uncomplicated AOM with otorrhea of less than 3 weeks' duration in one or both ears	N=599 21 days	Primary: Clinical response to therapy at the TOC visit (21 days), microbiological response, and treatment failure rate Secondary: Time to cessation of otorrhea, and physicians' assessment of clinical response at each visit	Primary: CIPRO and DEX treatment was more effective than ofloxacin treatment for the primary efficacy variable of clinical cure at the TOC visit (90 vs 78%, respectively; P=0.0025). Microbiologic eradication was greater with CIPRO and DEX than ofloxacin at the TOC visit (92 and 82%, respectively; P=0.0061). There were significantly fewer treatment failures in patients who were treated with CIPRO and DEX (4%) compared to ofloxacin (14%; P=0.0017). Secondary: There was a significant difference in the median time to cessation of otorrhea with CIPRO and DEX (four days) compared to ofloxacin (six days; P=0.0209). The physicians' assessment of clinical response at each visit showed significantly greater cure rates with CIPRO and DEX at day three (P=0.0001), day 11 (P=0.0001), and day 18 (P=0.0023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The adverse-event profiles of CIPRO and DEX and ofloxacin are similar. No serious treatment-related adverse events were reported during the study. Adverse events were generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Similar types of adverse events were noted in pediatric patients who were treated in both treatment groups.
Spektor et al.[117] (2017) Ciprofloxacin 0.3%, plus fluocinolone acetonide 0.025% otic solution vs ciprofloxacin 0.3% otic solution alone vs fluocinolone acetonide 0.025% otic solution alone Treatments were given twice daily for 7 days	Two twin DB, MC, RCTs Children between 6 months and 12 years of age with acute otitis media with tympanostomy tubes in at least 1 ear who presented with otorrhea for 3 weeks or less and with moderate or severe purulent otorrhea at inclusion	N=662 3 weeks	Primary: Time to cessation of otorrhea Secondary: Sustained microbiological cure, defined as eradication or presumed eradication at end-of-therapy and test-of-cure visits	Primary: The overall median time to cessation of otorrhea in patients receiving ciprofloxacin plus fluocinolone was 4.23 days (95% CI, 3.65 to 4.95 days) compared with 6.95 days (95% CI, 5.66 to 8.20 days) in those receiving ciprofloxacin alone (P<0.001). Although the median time to cessation of otorrhea for the fluocinolone group was not estimable because the number of censored patients was greater than the number of patients with cessation of otorrhea, the comparison vs ciprofloxacin plus fluocinolone revealed a statistically significant difference in favor of the combination (P<0.001). Secondary: The clinical cure rate at the test-of-cure visit was 80.6% in the ciprofloxacin plus fluocinolone group, 67.4% in the ciprofloxacin group (difference, 13.2%; 95% CI, 5.0 to 21.4%; P=0.002), and 47.6% in the fluocinolone group (difference, 33.0%; 95% CI, 24.0 to 42.0%; P<0.001). The sustained microbiological cure rate was 79.7% in the ciprofloxacin plus fluocinolone group vs 67.7% in the ciprofloxacin group (difference, 12.0%; 95% CI, 0.8 to 23.0%; P=0.04) and 37.6% in the fluocinolone group (difference, 42.1%; 95% CI, 29.3 to 54.8%; P<0.001). Only seven (3.1%) of the patients receiving ciprofloxacin plus fluocinolone, eight (3.6%) of the patients receiving ciprofloxacin, and 10 (4.7%) of the patients receiving fluocinolone presented with adverse events related to study medication.
Goldblatt et al.[118] (1998) Ofloxacin 0.3% otic solution BID for 10 days vs	MC, PG, RCT Patients 1 to 12 years of age with tympanostomy tubes and acute purulent otorrhea of presumed	N=474 10 days	Primary: Overall clinical response (cure or failure, defined as the absence or presence of otorrhea), microbiologic	Primary: There was no significant difference in the overall clinical cure rates among patients receiving ofloxacin (76%) compared to patients receiving amoxicillin-clavulanic acid (69%; P=0.169). Within the microbiologically evaluable population, a significantly higher percentage of ofloxacin-treated patients (96%) had an overall microbiologic response than did amoxicillin-clavulanic acid-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin-clavulanic acid oral suspension 40 mg/kg/day	bacterial origin for <3 weeks		outcomes, safety Secondary: Not reported	patients (67%; P<0.001). Pathogen persistence occurred in one ofloxacin-treated patient (1%) and 26 amoxicillin-clavulanic acid-treated patients (28%). There was recurrence in two ofloxacin-treated patients (2%) and four amoxicillin-clavulanic acid treated patients (4%). Reinfection was noted in only one subject, in the amoxicillin-clavulanic acid treatment arm (1%). There were significantly higher eradication rates in the ofloxacin-treated group than in the amoxicillin-clavulanic acid-treated group for *S aureus* and for *P aeruginosa*. Equivalent eradication rates occurred in the two treatment groups for *S pneumoniae*, *H influenzae,* and *M catarrhalis*. Overall clinical: microbiologic success (both clinical cure and microbiologic eradication) was 77% (64:83) for the ofloxacin-treated patients and 67% (62:93) for the amoxicillin-clavulanic acid-treated group. There was no significant difference among the treatment groups. A significantly lower percentage of adverse events occurred in ofloxacin-treated patients (42%) than in amoxicillin-clavulanic acid-treated patients (52%; P=0.043). The most commonly reported adverse events were rhinitis, fever, diarrhea, coughing and upper respiratory tract infection. Most of these were mild or moderate in severity. A significantly lower percentage of ofloxacin-treated patients (6%) experienced adverse events that were considered possibly or probably related to study medication than amoxicillin-clavulanic acid-treated patients (31%; P<0.001). A significantly higher percentage of amoxicillin-clavulanic acid-treated patients than of ofloxacin-treated patients experienced treatment-related diarrhea (27 vs 1%; P<0.001), treatment-related rash (5 vs 1%; P=0.022), or treatment-related moniliasis (3 vs 0%; P=0.015). Secondary: Not reported
Periodontitis				
Caton et al.[119] (2000)	DB, PC, RCT Patients aged 30 to	N=190 9 months	Primary: Change in clinical attachment level	Primary: In tooth sites with mild-to-moderate disease, improvements in attachment from baseline were demonstrated in both groups at all post-baseline time

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DOXY 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	75 years with evidence of periodontitis (at least 2 tooth sites within each of 2 qualifying quadrants with probing depth and clinical attachment level between 5 and 9 mm, inclusive, that bled on probing)		and probing depth, microbial outcomes Secondary: Not reported	points. The per-patient attachment gains were significantly greater with adjunctive DOXY at months three, six, and nine than with adjunctive placebo (P<0.05). After nine months of treatment, the mean attachment gains were 1.03 mm and 0.86 mm for the DOXY and the placebo groups, respectively (P<0.05). In tooth sites with severe disease (baseline probing depth ≥7 mm), improvements in attachment were demonstrated for both treatment groups at all time points. The per-patient attachment gains were significantly greater with DOXY than placebo (P<0.05). In tooth sites with mild-to-moderate disease, reductions in probing depth from baseline were demonstrated for both treatment groups. The per-patient reductions in probing depth were significantly greater for the DOXY group at every post-baseline time point than for placebo (P<0.005). In tooth sites with severe disease (baseline probing depth ≥7 mm), treatment with DOXY significantly reduced probing depth compared to treatment with placebo at all time points (P<0.01). Treatment with DOXY also significantly reduced probing depth in tooth sites with no disease compared to placebo (P<0.01). Small (<6%) but significant differences in the proportions of spirochetes present at months three, six, and nine of the treatment period were demonstrated between the DOXY and placebo groups (P<0.05), with lower proportions of small, intermediate, and large spirochetes present in the DOXY group than in the placebo group. There were no significant differences between the treatment groups in the proportions of other cellular morphotypes. There were no significant differences between treatment groups in total cultivable anaerobic flora or periodontal pathogens. Secondary: Not reported
Caton et al.[120] (2001)	DB, PC, RCT	N=151	Primary: Probing depth,	Primary: During active treatment (months three, six, and nine), per-patient

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
DOXY 20 mg BID for 9 months vs placebo At the baseline visit, scaling and root planing was performed on the qualifying quadrants until the tooth and root surfaces were free from deposits as determined by visual or tactile examination.	Patients aged 30 to 75 years with evidence of periodontitis (at least 2 tooth sites within each of 2 qualifying quadrants with probing depth and clinical attachment level between 5 and 9 mm, inclusive, that bled on probing)	12 months	clinical attachment level, adverse events, microbial outcomes Secondary: Not reported	reductions in probing depth from baseline were significantly greater for the DOXY group than for the placebo group (P<0.05). The incremental reductions in probing depth demonstrated in the DOXY group over nine months of active treatment were maintained through three additional months of no treatment (month 12). For tooth sites with mild to-moderate disease, reductions in probing depth from baseline were significantly greater for the DOXY group than for the placebo group at months three and nine of active treatment, and at the end of the no-treatment follow-up (month 12; P<0.05). Statistically significant treatment differences favoring DOXY over placebo were demonstrated between the treatment groups at months three and six of active treatment (P<0.05). Improvements in clinical attachment level demonstrated in the DOXY group during active treatment were maintained three months posttreatment (month 12); however, this difference was not statistically significant. During the three-month follow-up, the most frequent adverse events reported by more than one patient in a treatment group were headache, backache, toothache, sinus congestion and periodontal abscess. The incidence of adverse events was similar between the treatment groups. No deaths, serious adverse events, or discontinuations owing to adverse events were reported in either treatment group. Examination of microbial samples by darkfield microscopy revealed no differences in the proportions of selected bacterial morphotypes between the treatment groups in samples taken from the scaling and root planing quadrants at month 9 (end of active treatment) and month 12 (end of no-treatment followup). No significant differences were demonstrated between the DOXY group and the placebo group in the posttreatment composition of the normal flora (P>0.05). No differences were detected in the recovery of either periodontal pathogens (P>0.05) or opportunistic pathogens (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Deo et al.[121] (2010) DOXY 20 mg BID vs placebo All patients underwent scaling and root planing prior to receiving study treatment.	PC, PG, RCT Patients with periodontitis and type 2 diabetes mellitus	N=20 6 months	Primary: Probing pocket depth, clinical attachment level, and gingival recession Secondary: Not reported	Primary: The mean probing pocket depth reduction was 3.06 mm with DOXY and 2.54 mm with placebo (P<0.05). The mean clinical attachment level gain was 2.25 mm with DOXY and 1.58 mm with placebo (P<0.05). The mean increase in gingival recession was 0.80 mm in the DOXY group and 0.93 mm in the placebo group (P<0.05). Secondary: Not reported
Gapski et al.[122] (2010) DOXY 20 mg BID vs placebo Patients received full mouth scaling and root planing within 90 days before randomization. They also received access flap surgery in a minimum of one sextant.	DB, MC, PC, RCT Patients with chronic severe periodontitis with at least three teeth in the same sextant demonstrating both probing depth and clinical attachment level ≥5 to ≤12 mm and bleeding on probing with at least 10 teeth in the functional dentition	N=70 12 months	Primary: Clinical attachment levels, probing depth, bleeding on probing, gingival crevicular fluid bone marker assessment Secondary: Not reported	Primary: *Pooled surgical sites* Both placebo and DOXY groups demonstrated a significant reduction in probing depth compared to baseline; however, there were no significant differences between the groups. Surgical therapy resulted in mean clinical attachment level gains in both groups (P<0.05). DOXY-treated patients demonstrated a significant reduction in GCF ICTP levels compared to placebo immediately after the surgery (two months; P=0.03). *Moderate sites (baseline probing depth 5 to 6 mm)* There were significant reductions in probing depth and gains in clinical attachment level compared to baseline for the DOXY and placebo groups. The DOXY group demonstrated a significant decrease in the expression of GCF ICTP levels compared to placebo immediately after the surgery (two months; P=0.001). There was a significant reduction in percentage of bleeding on probing sites at three months between DOXY and placebo (P=0.02). Both DOXY and placebo showed comparable levels in percentage of sites bleeding on probing after the patients discontinued drug therapy (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Deep sites (baseline probing depth ≥7 mm) Greater reductions in probing depth were noted for both DOXY and placebo. DOXY resulted in greater reductions in probing depth compared to controls at three months (P=0.004). DOXY-treated patients demonstrated a significant increase in clinical attachment level compared to placebo during the drug administration (three months; P=0.02; six months; P=0.005). Secondary: Not reported
Preshaw et al.[123] (2004) DOXY 20 mg BID with scaling and root planing vs placebo with scaling and root planing	DB, MC, RCT Patients with moderate to severe chronic periodontitis	N=209 9 months	Primary: Changes in clinical attachment level and probing depth from baseline, and the total number of sites with attachment gains and probing depth reductions ≥2 mm and ≥3 mm from baseline Secondary: Not reported	Primary: Improvements in clinical attachment level and probing depth were greater following SRP with adjunctive DOXY than scaling and root planing with placebo, achieving statistical significance in all baseline disease categories at month nine (P<0.05). At month nine, 42.3% of sites in the DOXY group demonstrated clinical attachment level gain ≥2 mm compared to 32.0% of sites in the placebo group (P<0.01). CAL gain ±3 mm was seen in 15.4% of sites in the DOXY group compared to 10.6% of sites in the placebo group (P<0.05). When considering the same thresholds of change in probing depth, 42.9% of sites in the DOXY group compared to 31.1% of sites in the placebo group demonstrated probing depth reduction ±2 mm (P<0.01), and 15.4% of sites in the DOXY group compared to 9.1% of sites in the placebo group demonstrated probing depth reduction ±3 mm (P<0.01). Secondary: Not reported
Haffajee et al.[124] (2007) DOXY 20 mg BID for 12 weeks vs azithromycin 500	RCT, SB Patients with chronic periodontitis	N=92 1 year	Primary: Clinical parameters Secondary: Not reported	Primary: There were statistically significant improvements over time for most parameters, irrespective of treatment group, with the greatest improvements between baseline and three months post-therapy. All groups showed clinical improvements at 12 months, with patients receiving adjunctive agents showing a somewhat better response. All treatment groups showed statistically significant reductions in mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD for 3 days vs metronidazole 250 mg TID for 14 days (MET) vs scaling and root planing				pocket depth reduction and attachment-level gain over time. Patients receiving either systemically administered azithromycin or metronidazole showed greater mean pocket depth reduction post-therapy compared to patients in the DOXY- and SRP-only groups. The differences among treatment groups were statistically significant at 6 and 12 months. After adjusting for multiple comparisons, metronidazole was significantly different from DOXY at 12 months (P<0.05) and the metronidazole group was also significantly different from the SRP group at six months (P<0.05) and 12 months (P<0.01). The greatest improvement in mean attachment level post-therapy at initially deeper sites was observed for the metronidazole group, and the antibiotic groups showed greater improvement than the DOXY and scaling and root planing groups. Differences among treatment groups were significant at 12 months and approached significance at six months. Metronidazole was significantly different from scaling and root planing (P<0.05) at 12 months after adjusting for multiple comparisons. Patients showed attachment loss at 12 months ranging from 15 to 39% of patients in the DOXY and scaling and root planing only groups respectively. Secondary: Not reported
Prophylaxis of Ophthalmia Neonatorum				
Ali et al.[125] (2007) Erythromycin 0.5% ointment applied to eyes during the first few hours of birth vs betadine 2.5% applied to eyes	RCT Healthy newborns without congenital eye abnormalities from mothers who had not used any form of antibiotics within the last 48 hours prior to delivery, without rupture of	N=330 14 days	Primary: Rate of conjunctival symptoms Secondary: Not reported	Primary: The betadine group and erythromycin group had significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours through two weeks of birth when compared to the group that did not receive prophylaxis (9.0 and 18.4 vs 22.4%, respectively; P=0.030). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
during the first few hours of birth vs no prophylaxis	membranes for more than 18 hours and absence of meconium aspiration			
Bell et al.[126] (1993) Erythromycin 0.5% ointment applied to eyes of child at birth vs silver nitration applied to eyes of child at birth vs no prophylaxis	DB, RCT Women from the University of Washington Medical Center-associated obstetric clinics	N=669 60 days	Primary: Frequency of conjunctivitis and duration of prophylaxis Secondary: Not reported	Primary: After two months of observation it was found that infants who received prophylaxis had lower rates of conjunctivitis, with only silver nitrate showing a statistically significant decrease. Rates of conjunctivitis were 22% in the no prophylaxis group, 16% in the erythromycin group and 14% in the silver nitrate group (P value not reported). Patients who received silver nitrate at birth had a 39% lower rate of conjunctivitis (HR, 0.61; 95% CI, 0.39 to 0.97), while those who received erythromycin had a 31% lower rate of conjunctivitis (HR, 0.69; 95% CI, 0.44 to 1.07). When cases of conjunctivitis were compared before and after two weeks of birth, the protective effect of prophylaxis was found to be most effective prior to two weeks of birth. The efficacy of erythromycin from days zero to 14 was 9.0% as compared to 15.0% with no prophylaxis (P=0.050). This was not found to be statistically significant from days 15 to 60 (7.0 vs 8.0%, respectively; P=0.920). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study design abbreviations: AC=active comparator, DB=double blind, MA=meta-analysis, MC=multicenter, NI=non inferiority, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind
Miscellaneous abbreviations: AOE=acute otitis externa, AOM=acute otitis media, BAC=bacitracin, CI=confidence interval, CIPRO=ciprofloxacin, DEX=dexamethasone, DOXY=doxycycline, EOT=end-of-treatment, HYDRO=hydrocortisone, HR=hazard ratio, IOP=intraocular pressure, GCF ICTP=gingival crevicular fluid type 1 collagen carboxyterminal peptide, ITT=intention-to-treat, MIC=minimum inhibitory concentration, MITT=modified intention-to-treat, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-sensitive *Staphylococcus aureus*, NNT=number needed to treat, OR=odds ratio, POLY=polymyxin B, RR=relative risk, SD=standard deviation, TOBY=tobramycin, TOC=test-of-cure

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 13. Relative Cost of the EENT Antibacterials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Azithromycin	solution*	AzaSite®	$$$$	N/A
Bacitracin	ointment*	N/A	N/A	$$
Besifloxacin	suspension*	Besivance®	$$$$$	N/A
Ciprofloxacin	ointment*, solution*§‡, suspension†	Ciloxan®§	$$$$$	$
Doxycycline	tablet	N/A	N/A	$
Erythromycin base	ointment*	N/A	N/A	$
Gatifloxacin	solution*	Zymaxid®*	$$$$	$$
Gentamicin	ointment*, solution*	N/A	N/A	$
Levofloxacin	solution*	N/A	N/A	$$
Moxifloxacin	solution*	Vigamox®§	$$$$	$
Ofloxacin	solution*†	Ocuflox®§	$$$$	$
Sulfacetamide	ointment*, solution*	N/A	$$	$$
Tobramycin	ointment*, solution*	Tobrex®§ ointment	$$$$$	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Combination Products				
Bacitracin and polymyxin B	ointment*	N/A	N/A	$
Ciprofloxacin and dexamethasone	suspension†	Ciprodex®	$$$$	$$$$
Ciprofloxacin and fluocinolone	solution†	Otovel®§	$$$$$	$$$$
Ciprofloxacin and hydrocortisone	suspension†	Cipro HC®	$$$$$	N/A
Gentamicin and prednisolone	ointment*, suspension*	Pred-G® ointment	$$$$	N/A
Neomycin, bacitracin and polymyxin B	ointment*	N/A	N/A	$$
Neomycin, bacitracin, polymyxin B and hydrocortisone	ointment*	N/A	N/A	$$
Neomycin, colistin, hydrocortisone and thonzonium	suspension†	Cortisporin-TC®	$$$$$	N/A
Neomycin, polymyxin B and dexamethasone	ointment*, suspension*	Maxitrol®§	$$$$	$
Neomycin, polymyxin B and gramicidin	solution*	N/A	N/A	$$
Neomycin, polymyxin B and hydrocortisone	solution†, suspension*†	N/A	N/A	$$$
Polymyxin B and trimethoprim	solution*	Polytrim®§	$$$	$
Sulfacetamide and prednisolone	ointment*, solution*§, suspension*	Blephamide® ointment	$$$$$	$
Tobramycin and dexamethasone	ointment*, suspension*	TobraDex®§, TobraDex ST®	$$$$	$$$
Tobramycin and loteprednol	suspension*	Zylet®	$$$$$	N/A

*Ophthalmic formulation.
†Otic formulation.
§Generic is available in at least one dosage form and/or strength.
N/A=not available.

X. Conclusions

The eye, ear, nose, and throat (EENT) antibacterials effectively treat a variety of infections.[1-26] There is at least one single entity ophthalmic aminoglycoside, macrolide, quinolone, sulfonamide, and miscellaneous antibacterial available in a generic formulation. There are several ophthalmic and otic antibacterial-corticosteroid combination products available in a generic formulation.

For the treatment of blepharitis, guidelines recommend initial pharmacological treatment with bacitracin or erythromycin ointment. Corticosteroids may also be used to control inflammation and maintain patient comfort; however, adverse effects (increased intraocular pressure and cataracts) should be considered.[27,28] Bacterial conjunctivitis is often a self-limiting condition and resolves spontaneously without specific treatment.[29,30] The use of topical antibacterial therapy may lead to earlier clinical and microbiological remission. The choice of antibiotic is usually empirical and guidelines do not give preference to one ophthalmic antibacterial agent over another.[29,43] However, soft contact lens wearers with conjunctivitis have a high incidence of infection with *Pseudomonas* and quinolones are the preferred treatment option in this patient population.[30] Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. Guidelines recommend empiric treatment with

cefazolin, vancomycin, or a quinolone if the organism is unknown or if multiple types of organisms are identified.[33] Numerous clinical trials have demonstrated similar clinical cure rates with the ophthalmic antibacterial agents.[46-79,90-101,125,126]

For the treatment of acute otitis externa, guidelines recommend the use of a topical antibacterial agent; however, they do not give preference to agent over another as there is minimal or no difference in clinical or bacteriologic cure rates among the agents.[35] Topical preparations that contain alcohol or have a low pH, as well as aminoglycosides, should be avoided in patients with tympanostomy tubes or perforated tympanic membranes due to the risk of ototoxicity.[35,127] Guidelines recommend the use of an oral antibacterial agent for the treatment of acute otitis media.[35,38,45] Topical antibacterials may be used as an alternative treatment option in patients with perforated tympanic membranes, tympanostomy tubes, or chronic suppurative otitis media.[39,40] Several clinical trials have demonstrated similar cure rates with the otic antibacterials. Relatively few studies have demonstrated greater efficacy with one agent over another.[102-118]

Doxycycline is approved for use as an adjunct to scaling and root planing to promote attachment level gain and reduce pocket depth in adult patients with periodontitis.[1,26] Studies have shown that the adjunctive use of doxycycline with scaling and root planing was more effective than scaling and root planing alone.[119-124] Doxycycline (subantimicrobial dose) is available in a generic formulation.

There is insufficient evidence to support that one brand EENT antibacterial is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT antibacterials within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (EENT) antibacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Eye, Ear, Nose, and Throat Preparations: Vasoconstrictors
AHFS Class 523200
August 10, 2022

I. Overview

The eye, ear, nose, and throat (EENT) vasoconstrictors constrict the arterioles and reduce blood flow and are approved for use in a variety of ophthalmic conditions/procedures. The ocular formulations are frequently used for the temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye. They are also used as a mydriatic in ophthalmic conditions and procedures.[1-4]

The EENT vasoconstrictors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Phenylephrine is currently the only agent, and it is available in a generic formulation. This class was last reviewed in May 2020.

Table 1. EENT Vasoconstrictors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Phenylephrine	solution†‡	N/A	phenylephrine

†Ophthalmic formulation.
‡Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the eye, ear, nose, and throat (EENT) vasoconstrictors are summarized in Table 2.

Table 2. Treatment Guidelines Using the EENT Vasoconstrictors

Clinical Guideline	Recommendation(s)
Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)[5]**	Pharmacologic treatment of allergic rhinitis • New-generation oral H_1-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis. • New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines. • In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral H_1-antihistamines not be used to prevent wheezing or asthma. • Intranasal H_1-antihistamines are suggested in adults and children with seasonal allergic rhinitis. • New-generation oral H_1-antihistamines are suggested over intranasal H_1-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis. • Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis. • Oral H_1-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis. • Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis. • For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are

Clinical Guideline	Recommendation(s)
	suggested over oral H_1-antihistamines in adults and children. • Intranasal glucocorticosteroids are recommended over intranasal H_1-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis. • For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested. • Intramuscular glucocorticosteroids are not recommended for allergic rhinitis. • Intranasal chromones are suggested for allergic rhinitis, and intranasal H_1-antihistamines are suggested over intranasal chromones. • Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis. • A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children. • It is suggested that regular use of oral decongestants, either alone or in combination with an oral H_1-antihistamine, not occur in patients with allergic rhinitis. • Intraocular H_1-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis.
American Academy of Allergy, Asthma & Immunology: **Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision (2016)[6]**	<u>Should a combination of an oral H_1-antihistamine and intranasal corticosteroid vs intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an oral H_1-antihistamine or an intranasal corticosteroid alone is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid alone rather than a combination of an intranasal corticosteroid with an oral H_1-antihistamine is suggested (very low certainty of evidence). • This recommendation concerns regular use of newer and less sedative oral H_1-antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis. For older oral H_1-antihistamines with more sedative effects, the balance of desirable and undesirable effects may be different. • Currently available evidence suggests that there is no additional benefit from a combination therapy compared with intranasal corticosteroid alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal corticosteroid alone be used for treatment of allergic rhinitis?</u> • In patients with seasonal allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, either a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine or an intranasal corticosteroid alone is suggested (very low certainty of evidence). • At initiation of treatment (approximately the first two weeks), a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine might act faster than an intranasal corticosteroid alone and thus might be preferred by some patients. The choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. <u>Should a combination of an intranasal H_1-antihistamine and intranasal corticosteroid vs an intranasal H_1-antihistamine alone be used for treatment of allergic rhinitis?</u>

Clinical Guideline	Recommendation(s)
	• In patients with seasonal allergic rhinitis, a combination of an intranasal corticosteroid with an intranasal H_1-antihistamine rather than an intranasal H_1-antihistamine alone is suggested (low certainty of evidence). Should a leukotriene receptor antagonist vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either a leukotriene receptor antagonist or an oral H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an oral H_1-antihistamine rather than a leukotriene receptor antagonist is suggested (low certainty of evidence). • The choice of a leukotriene receptor antagonist or oral H_1-antihistamine will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an oral H_1-antihistamine might still be more cost-effective, but this will largely depend on availability of generic leukotriene receptor antagonists and the local cost of various newer-generation oral H_1-antihistamines and leukotriene receptor antagonists. • Some patients with allergic rhinitis who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from a leukotriene receptor antagonist more than from an oral H_1-antihistamine. However, this recommendation applies to treatment of allergic rhinitis but not to treatment of asthma. Patients with asthma who have concomitant allergic rhinitis should receive an appropriate treatment according to the guidelines for the treatment of asthma. Should an intranasal H_1-antihistamine vs an intranasal corticosteroid be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (moderate certainty of evidence). • In patients with perennial allergic rhinitis, an intranasal corticosteroid rather than an intranasal H_1-antihistamine is suggested (low certainty of evidence). Should an intranasal H_1-antihistamine vs an oral H_1-antihistamine be used for treatment of allergic rhinitis? • In patients with seasonal allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (low certainty of evidence). • In patients with perennial allergic rhinitis, either an intranasal H_1-antihistamine or oral H_1-antihistamine is suggested (very low certainty of evidence). • The choice of treatment will depend mostly on patient preferences, local availability, and cost of treatment.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[7]	Pharmacologic therapy • The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age. Oral antihistamines • First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. • First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents. • Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime. • The anticholinergic effects of the first-generation antihistamines may explain the

Clinical Guideline	Recommendation(s)
	reported better control of rhinorrhea compared with the second-generation antihistamines. • The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. • Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. • Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects. • Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines. • With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • No single second-generation antihistamine has been conclusively shown to have greater efficacy. <u>Intranasal antihistamines</u> • Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. • Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption. • Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. • Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. <u>Oral decongestants</u> • Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. • The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone. • Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine. • Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established. • Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension. • Concomitant use of caffeine and stimulants may be associated with an increase in adverse events. • Oral decongestants should be used with caution in older adults and young

Clinical Guideline	Recommendation(s)
	children, and in patients of any age with a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. • Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age. <u>Topical decongestants</u> • Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa. <u>Intranasal corticosteroids</u> • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. • Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies. • The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported. <u>Oral corticosteroids</u> • A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. • Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. <u>Intranasal cromolyn</u> • Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. • Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines. <u>Intranasal anticholinergics</u> • Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms. • Dryness of the nasal membranes may occur with intranasal anticholinergics. • The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events. <u>Oral antileukotriene agents</u> • Oral antileukotriene agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. <u>Omalizumab</u>

Clinical Guideline	Recommendation(s)
	• Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma. Nasal saline • Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy. Over-the-counter cough and cold medications for young children • The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years. • Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma, and Immunology/ Joint Council on Allergy, Asthma, and Immunology: **Treatment of seasonal allergic rhinitis, an evidence-based focused 2017 guideline update (2017)**[8]	For initial treatment of nasal symptoms of seasonal allergic rhinitis in patients ≥12 years of age: • Routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine. • An intranasal corticosteroid is recommended over a leukotriene receptor antagonist (for ≥15 years of age). • For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine.
American Academy of Allergy, Asthma & Immunology: **Rhinitis 2020: A practice parameter update (2020)**[9]	• Prescribing first-generation antihistamines is not recommended; a second-generation antihistamine is preferred when prescribing an oral antihistamine for the treatment of AR. • Clinician should not select the oral LTRA montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies. • Clinicians should not select an oral LTRA for the treatment of NAR. • For the treatment of very severe or intractable AR, the clinician may consider a short course (5 to 7 days) of oral corticosteroids. • For the treatment of very severe or intractable AR, the clinician should not prescribe a depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects. • The clinician should offer intranasal antihistamine as an initial treatment option for patients with SAR. • The clinician should offer intranasal antihistamine as a first-line monotherapy option for patients with NAR. • The clinician should offer intranasal antihistamine as a first-line option for patients with intermittent AR. • When choosing monotherapy for persistent AR, intranasal corticosteroid should be the preferred medication. • For the initial treatment of moderate/severe SAR in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over an LTRA. • The use of intranasal decongestants should be short term and be used for intermittent or episodic therapy of nasal congestion. • In patients having severe mucosal edema, which impairs the delivery of other intranasal agents, an intranasal decongestant should be considered for up to five

Clinical Guideline	Recommendation(s)
	days of use. • Oral decongestant agents should be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome. • Oral decongestants should be avoided during the first trimester of pregnancy. • Patients with PAR and NAR who have rhinorrhea as their main nasal symptom should be offered intranasal ipratropium. • Intranasal cromolyn should be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures. • Clinicians should consider the combination of an intranasal corticosteroid and an internasal antihistamine for the initial treatment of moderate/severe nasal symptoms of SAR in patients age ≥12 years. • Clinicians should consider the combination of an intranasal corticosteroid and an intranasal antihistamine for moderate/severe SAR, PAR and NAR that is resistant to pharmacologic monotherapy. • For patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium. • Patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to four weeks. • For patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician should consider the addition of pseudoephedrine, when tolerated. • For SAR, the clinician should not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine. • The clinician should not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients ≥12 years of age with symptoms of SAR. • Clinicians should not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR. • The addition of the oral LTRA montelukast to an intranasal corticosteroid for AR is not recommended. • Clinicians should offer an intranasal corticosteroid as a first-line therapy for NAR. • Clinicians should offer an intranasal antihistamine as a first-line therapy for NAR. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be offered through shared decision making to patients with moderate/severe AR who are not controlled with allergen avoidance and/or pharmacotherapy or choose immunotherapy as the preferred method of treatment and/or desire the potential benefit of immunotherapy to prevent or reduce the severity of comorbid conditions, such as asthma. • Allergen immunotherapy (subcutaneous or sublingual tablets) should be considered for patients with controlled mild and moderate asthma with coexisting AR.
American Academy of Otolaryngology - Head and Neck Surgery Foundation: **Clinical Practice Guideline**	• The clinical diagnosis of allergic rhinitis (AR) should be made when patients present with a history and physical exam consistent with an allergic cause and one or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes.

Clinical Guideline	Recommendation(s)
Allergic Rhinitis (2015)[10]	• Patients with a clinical diagnosis or AR who do not respond to empiric treatment, or in whom the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy, should have specific IgE (skin or blood) allergy testing. • Sinonasal imaging should not routinely be performed in patients presenting with symptoms consistent with a diagnosis or AR. • AR patients who have identified allergens that correlate with clinical symptoms may avoid known allergens or utilize environmental controls. • Patients with AR should be assessed for the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. • Intranasal steroids are recommended for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. • Oral second-generation/less-sedating antihistamines are recommended for patients with AR and primary complaints of sneezing and itching. • Intranasal antihistamines may be used in patients with seasonal, perennial, or episodic AR. • Oral leukotriene receptor antagonists should not be offered as primary therapy for patients with AR. • Combination pharmacologic therapy may be used in patients with AR who have inadequate response to pharmacologic monotherapy. • Immunotherapy (sublingual or subcutaneous) should be offered to patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.
American Academy of Ophthalmology Preferred Practice Pattern Guidelines: **Conjunctivitis (2018)[11]**	<u>Seasonal allergic conjunctivitis</u> • Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine H_1- receptor antagonists. • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent. • Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease. • The use of topical mast-cell inhibitors can also be helpful in alleviating the symptoms of allergic rhinitis. Mast-cell inhibitors formulated as a nasal spray and aerosols are also helpful in alleviating the symptoms of allergic rhinitis and asthma in some patients. • If the symptoms are not adequately controlled, a brief course (one to two weeks) of a topical corticosteroid with a low side effect profile can be added to the regimen. • Oral antihistamines are commonly used but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and actually worsen allergic conjunctivitis. • Concomitant use of cooled artificial tears may alleviate coexisting tear deficiency and dilute allergens and inflammatory mediators on the ocular surface. • In severe cases, topical cyclosporine or tacrolimus can be considered. <u>Vernal/atopic conjunctivitis</u> • General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants. • Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. • Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations. • Topical cyclosporine (2.0%) is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to

Clinical Guideline	Recommendation(s)
	topical therapy, supratarsal injection of corticosteroid can be considered. Systemic immunosuppression is rarely warranted, but options include montelukast, aspirin, interferons, and oral T-cell inhibitors, such as cyclosporine and tacrolimus. • In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma.
College of Optometrists: **Clinical Management Guideline on Bacterial Conjunctivitis (2021)**[12]	Etiology • Self-limiting bacterial infection of the conjunctiva, typically by: o *Staphylococcus* species o *Streptococcus pneumoniae* o *Haemophilus influenzae* o *Moraxella catarrhalis* Predisposing factors • Children and the elderly have an increased risk of infective conjunctivitis o contamination of the conjunctival surface o superficial trauma o contact lens wear (infection may be Gram-negative) o secondary to viral conjunctivitis o diabetes (or other disease compromising the immune system) o steroids (systemic or topical, compromising ocular resistance to infection) o blepharitis (or other chronic ocular inflammation) Symptoms • Acute onset of: o redness o discomfort, usually described as burning or grittiness o discharge (may cause temporary blurring of vision) o crusting of lids (often stuck together after sleep and may have to be bathed open) • Usually bilateral – one eye may be affected before the other (by one or two days) Management by optometrist • Practitioners should recognize their limitations and where necessary seek further advice or refer the patient elsewhere • Non pharmacological o Often resolves in five to seven days without treatment o Bathe/clean the eyelids with proprietary sterile wipes, lint or cotton wool dipped in sterile saline or boiled (cooled) water to remove crusting o Advise patient that condition is contagious (do not share towels, etc.) • Pharmacological o Treatment with topical antibiotic may improve short-term outcome and render patient less infectious to others o Topical antibiotics (with no evidence of superiority of particular antibiotics) may include: chloramphenicol 0.5% eye drops, chloramphenicol 1% ointment, azithromycin 1.5% eye drops, fusidic acid 1% viscous eye drops (note high cost and narrower spectrum of activity than chloramphenicol) o Predictors of bacterial culture positivity at presentation include purulent discharge and age less than five years o Contact lens wearers with a diagnosis of bacterial conjunctivitis should be treated with a topical antibiotic effective against Gram-negative organisms, e.g. a quinolone such as levofloxacin or moxifloxacin, or an aminoglycoside such as gentamicin. Contact lenses should not be worn during the treatment period o Advise patient to return/seek further help if symptoms persist beyond seven

Clinical Guideline	Recommendation(s)
	days Possible management by ophthalmologist • If resistant to treatment, or recurrent: ○ conjunctival swabs taken for microscopy and culture and/or polymerase chain reaction analysis ○ treatment with other antibiotics, based on culture results

III. Indications

The Food and Drug Administration (FDA)-approved indications for the eye, ear, nose, and throat (EENT) vasoconstrictors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the EENT Vasoconstrictors[1-4]

Indication	Phenylephrine
Ocular Vasoconstrictor	
To dilate the pupil	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the EENT Vasoconstrictors[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Phenylephrine	Variable (% not reported)	Not reported	Liver (% not reported)	Renal (80 to 86)	2 to 3

V. Drug Interactions

Major drug interactions with the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 5.

Table 5. Major Drug Interactions with the EENT Vasoconstrictors[3]

Generic Name(s)	Interaction	Mechanism
EENT Vasoconstrictors (phenylephrine)	Atropine	Concomitant use of phenylephrine and atropine may enhance the pressor effects and induce tachycardia in some patients.

VI. Adverse Drug Events

The most common adverse drug events reported with the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the EENT Vasoconstrictors[1-4]

Adverse Events	Phenylephrine
Cardiovascular	
Arrhythmia	✔
Hypertension	✔

Adverse Events	Phenylephrine
Myocardial infarction	✔
Subarachnoid hemorrhage	✔
Syncope	✔
Ocular	
Burning/stinging	✔
Floaters	✔
Irritation	✔
Rebound miosis	✔
Visual disturbances	✔

✔ Percent not specified.
-Incidence not reported.

VII. Dosing and Administration

The usual dosing regimens for the eye, ear, nose, and throat (EENT) vasoconstrictors are listed in Table 7.

Table 7. Usual Dosing Regimens for the EENT Vasoconstrictors[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Phenylephrine	Mydriasis: Ophthalmic solution: 1 drop every 3 to 5 minutes as needed, up to 3 drops per eye	Mydriasis (in patients <1 year of age): Ophthalmic solution (2.5% solution only): 1 drop every 3 to 5 minutes, up to 3 drops per eye Mydriasis (in patients ≥1 year of age): Ophthalmic solution (2.5% or 10%): 1 drop every 3 to 5 minutes, up to 3 drops per eye	Ophthalmic solution: 2.5% 10%

VIII. Effectiveness

There were no clinical trials identified in the medical literature that directly compared the safety and efficacy of the ophthalmic or nasal eye, ear, nose, and throat (EENT) vasoconstrictors.

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama

Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 8. Relative Cost of the Vasoconstrictors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Phenylephrine	solution†‡	N/A	N/A	$$

†Ophthalmic formulation.
‡Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

Phenylephrine ophthalmic solution is currently the only included agent, and it is available in a generic formulation. It is indicated to dilate the pupil.[1-4]

Treatment options for allergic rhinitis include anticholinergics, antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists, and mast cell stabilizers.[5-7,9,10] The selection of therapy should be individualized and take into consideration the severity and duration of the disease, patient preference, efficacy, and safety.[5] The intranasal corticosteroids are the most effective agents for the treatment of allergic rhinitis. Antihistamines treat rhinorrhea, sneezing, itching, and allergic conjunctivitis but have little effect on nasal congestion. They are also less effective than intranasal corticosteroids. Oral decongestants effectively treat nasal congestion; however, they may cause insomnia, irritability, and palpitations. Topical decongestants are also effective for the short-term treatment of nasal congestion. Chronic use of topical decongestants may cause rhinitis medicamentosa and should be avoided.[5-7]

The scientific evidence regarding the efficacy of the EENT vasoconstrictors is extremely limited. There is insufficient evidence to support that one brand EENT vasoconstrictor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand EENT vasoconstrictors within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand eye, ear, nose, and throat (EENT) vasoconstrictor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Androgens
AHFS Class 680800
August 10, 2022

I. Overview

The androgens are approved for a variety of indications, including hypogonadism and delayed puberty in males, endometriosis and fibrocystic breast disease in females, promotion of weight gain, relief of bone pain, and treatment of anemias.[1-18] Danazol is an oral synthetic derivative of ethisterone with a weak androgenic activity. It suppresses the pituitary-ovarian axis possibly by inhibiting the release of pituitary gonadotropins, altering sex steroid metabolism and interacting with sex hormone receptors. It reduces ovarian estrogen production by depressing the release of follicle-stimulating hormone and luteinizing hormone. Danazol may also have inhibitory effects at gonadal sites. It decreases concentrations of immunoglobulins (Ig) IgA, IgG, and IgM as well as phospholipids and IgG isotope autoantibodies in patients with endometriosis and hereditary angioedema. Danazol increases serum concentrations of C1 esterase inhibitor in patients with hereditary angioedema.[1,17,18] Methyltestosterone is an oral, synthetic, alkylated testosterone derivative with significant androgen activity.[1-18] Oxandrolone is an anabolic steroid. Oxandrolone suppresses gonadotropic functions of the pituitary gland and exhibits direct action on the testes. It also increases low-density lipoprotein and decreases high-density lipoprotein.[1-18] Testosterone is an endogenous androgen that plays a role in the normal growth and development of the male sex organs as well as the maintenance of secondary sex characteristics.[1,18]

With the exception of danazol and oxandrolone, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. The oral synthetic testosterone, methyltestosterone, and the injectable testosterone, testosterone enanthate, are also FDA-approved for the treatment of delayed puberty in males and metastatic mammary cancer in females. Danazol is FDA-approved for the treatment of endometriosis, fibrocystic breast disease, and hereditary angioedema, though it is not indicated for the management of male hypogonadism. Oxandrolone is approved for adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. This agent is also approved to offset the protein catabolism associated with prolonged administration of corticosteroids and for the relief of the bone pain frequently accompanying osteoporosis.[1-18] Testosterone undecanoate (Aveed®) was FDA approved in March 2014 and is a longer-acting injectable formulation of testosterone. Maintenance treatment occurs every 10 weeks; however, patients need to be observed for at least 30 minutes after injection due to the risk of serious pulmonary oil microembolism reactions and anaphylaxis. Aveed® includes a boxed warning regarding this risk and is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[13] A new dosage form of testosterone enanthate, Xyosted®, was approved in October 2018 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[12] Xyosted® is the first subcutaneous testosterone autoinjector product, and it dosed weekly.[12] Testosterone enanthate is also available generically as an intramuscular injection.[18] An oral formulation of testosterone undecanoate (Jatenzo®) was FDA approved in 2019 and is dosed twice daily.[16]

Hypogonadism is a defect of the reproductive system which results in a lack of function of the gonads (testes). It can be categorized by the level of the reproductive system that is defective.[19] Primary hypogonadism is hypogonadism resulting from a defect of the gonads while secondary hypogonadism, also known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary.[20] Male hypogonadism may manifest with testosterone deficiency and/or infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor ability to concentrate, and an increased risk of osteoporosis and fractures.[19] Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients. The oral alkylated androgens are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects.[19,21-31]

The androgens that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Danazol, methyltestosterone, oxandrolone, testosterone, testosterone cypionate, and testosterone enanthate are available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Androgens Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Danazol	capsule*	N/A	danazol
Methyltestosterone	capsule*, tablet	N/A	methyltestosterone
Oxandrolone	tablet*	N/A	oxandrolone
Testosterone	implant, nasal gel, transdermal gel, transdermal patch, transdermal solution	Androderm®, AndroGel®*, Fortesta®*, Natesto®, Testim®*, Testopel®, Vogelxo®*	testosterone
Testosterone cypionate	solution for injection	Depo®-Testosterone*	testosterone cypionate
Testosterone enanthate	solution for injection*	Xyosted®	testosterone enanthate
Testosterone undecanoate	capsule, oil for injection	Aveed®, Jatenzo®	none

*Generic is available in at least one dosage form or strength.
N/A=Not applicable, PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the androgens are summarized in Table 2.

Table 2. Treatment Guidelines Using the Androgens

Clinical Guideline	Recommendation(s)
The American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002)**[19]	• Testosterone replacement therapy should maintain testosterone levels within the physiologic range (280 and 800 ng/dL). • Testosterone replacement therapy can be used in men with hypogonadism who are not interested in fertility or who are not able to achieve fertility. • Treatment of men with hypogonadism with testosterone replacement therapy results in increased sexual interest and increased number of spontaneous erections. • Secondary sex characteristics (i.e., increased muscle mass, beard growth, growth of pubic and axillary hair and phallus growth) improve with testosterone replacement therapy. • In adolescent male patients with hypogonadotropic hypogonadism, testosterone replacement therapy increases bone mineral density in comparison with that in male patients with hypogonadism not receiving testosterone replacement therapy. In prepubertal-onset hypogonadotropic hypogonadism, diminished bone mass may be only marginally improved by testosterone replacement therapy. • No specific recommendations can be made on the possible normalization of growth hormone levels in elderly men with testosterone replacement therapy. Further research is needed to clarify the potential risks and benefits associated with therapy. • Whether testosterone replacement therapy in men with hypogonadism increases, decreases, or has a neutral effect on cardiovascular risk remains uncertain. • Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available in the Unites States are generally not recommended because of poor androgen effects, adverse lipid changes and hepatic side effects, such as hemorrhagic liver cysts, cholestasis and hepatocellular adenoma.
International Society	Clinical and laboratory diagnosis

Clinical Guideline	Recommendation(s)
for the Study of the Aging Male: **Recommendations: Diagnosis, Treatment and Monitoring of Hypogonadism in Men (2015)**[22]	• Hypogonadism (testosterone deficiency) in adult men is a clinical and biochemical syndrome associated with low level of testosterone, which may adversely affect multiple organ functions and quality of life. • The diagnosis of hypogonadism requires the presence of characteristic symptoms and signs in combination with decreased serum concentration of testosterone. Investigate hypogonadism in men with the following conditions: o Low libido o Poor morning erections o Erectile dysfunction o Depressed mood o Fatigue o Decreased vitality o Cognitive impairment o Insulin resistance o Obesity, abdominal obesity o Metabolic syndrome o Arterial hypertension o Diabetes mellitus type 2 o Decreased muscle mass and strength o Decreased bone mineral density and osteoporosis o Use of glucocorticoids, opioids, antipsychotics • Symptoms must be accompanied by decreased serum concentrations of total testosterone (TT) or free T level to support a diagnosis of symptomatic hypogonadism. • A recommended lower limit of normal for TT is 12.1 nmol/L. However, due to individual differences in testosterone sensitivity some men may exhibit symptoms of hypogonadism with TT concentrations above this threshold and may benefit from testosterone replacement therapy (TRT). TRT may be reasonably offered to symptomatic men with testosterone concentrations >12 nmol/L based on clinical judgment, and if free T concentrations are reduced. • Free T levels as low as 225 pmol/L (65 pg/mL) or 243 pmol/L (70 pg/mL) have been recommended as a lower limit of normal range and together with the presence of one or more hypogonadal symptoms can provide supportive evidence for TRT. • It is preferred to obtain a serum sample for TT determination between 07:00 and 11:00 am; although, diurnal variation is substantially blunted in older men. <u>Assessment of treatment outcome</u> • Improvement in hypogonadal signs and symptoms occur at different times for different organ systems. • Reduction in fat mass and increased lean body mass and muscle strength occur within 12 to 16 weeks of starting TRT and stabilize at six to 12 months but can continue to improve over years. • Significant improvement in libido is usually experienced within three to six weeks of commencing TRT. • Significant improvement in quality of life usually occurs within three to four weeks of starting TRT; longer-term TRT is required to achieve maximum quality of life benefit. • Effects on depressive mood become detectable after three to six weeks of starting TRT, with maximum improvement occurring after 18 to 30 weeks. • Improvements in bone are detectable after six months of TRT, while the full beneficial effect of TRT on bone mineral density may take two to three years or more. • Effects of TRT on lipids appear after four weeks, with maximal effects being seen after six to 12 months of treatment. Insulin sensitivity may improve within a

Clinical Guideline	Recommendation(s)
	few days of starting TRT, but effects on glycemic control become evident only after three to 12 months. • Failure to improve clinical symptoms within a reasonable period of time should result in reevaluation of TRT with regard to dosage, compliance and level of serum T achieved. Further investigation should be undertaken to determine other causes of the symptoms. <u>Treatment and delivery systems</u> • Currently available intramuscular, subdermal, transdermal, oral and buccal T preparations are safe and effective. • The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each TRT preparation. The selection of the TRT preparation should be a joint decision of an informed patient and physician. • Because the possible development of an adverse event during treatment (especially elevated hematocrit) requires rapid discontinuation of TRT, short-acting TRT preparations may be preferred over the long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism. • Periodic hematological assessment is, however, indicated, i.e. before TRT, then three to four months and 12 months in the first year of treatment, and annually thereafter. Although it is not yet clear what upper limit of hematocrit level is clinically desirable, dose adjustments may be necessary to keep hematocrit below 52 to 54%. • Inadequate data are available to determine the optimal target serum T level for men with late-onset hypogonadism. • Men with significant erythrocytosis (hematocrit >52%), severe untreated obstructive sleep apnea, or untreated severe congestive heart failure should not be started on treatment with TRT without prior resolution of the co-morbid condition.
The Endocrine Society: Clinical Practice Guidelines: **Testosterone Therapy in Men with Hypogonadism (2018)**[21]	• Testosterone replacement therapy is recommended in hypogonadal men to maintain secondary sex characteristics and correct symptoms of testosterone deficiency. • Initiating testosterone replacement therapy is recommended with any of the following regimens after evaluating patient preference, consideration of pharmacokinetics, treatment burden, cost: o Testosterone enanthate or cypionate: 75 to 100 mg intramuscular weekly; or 150 to 200 mg intramuscular every two weeks. o Testosterone 1%, 1.62%, or 2% gels: transdermal gel applied to skin; check package insert for application site and instructions. o Testosterone axillary solution: 60 mg of solution applied in the axillae o Testosterone patches: one or two patches, designed to nominally deliver 2 to 4 mg of testosterone during 24 hours applied every day on nonpressure areas. o Testosterone buccal: apply one 30 mg tablet to buccal mucosa every 12 hours. o Testosterone pellets implanted subcutaneously at intervals of three to six months; the dose and regimen vary with the formulation used. o Injectable long-acting testosterone undecanoate in oil: 750 mg intramuscular, followed by 750 mg at 4 weeks, and 750 mg every 10 weeks. o Nasal testosterone gel: 11 mg two or three times daily. • Clomiphene citrate has been used empirically in men with hypogonadotropic hypogonadism; however, neither its efficacy nor its safety has been demonstrated in randomized trials. • Testosterone therapy is not recommended in men planning fertility in the near

Clinical Guideline	Recommendation(s)
	term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen (PSA) level > 4 ng/mL, a PSA level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea (OSA), severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last six months, or thrombophilia. • Short-term testosterone replacement therapy may be considered as adjunctive therapy in human immunodeficiency virus-infected men with low testosterone levels and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. • In hypogonadal men who have started testosterone therapy, evaluate the patient after treatment initiation to assess whether the patient has responded to treatment, is suffering any adverse effects, and is complying with the treatment regimen.
American Society for Reproductive Medicine: **Treatment of Pelvic Pain Associated with Endometriosis: A Committee Opinion (2014)[23]**	• Both medical and surgical treatments for endometriosis are effective. • Oral contraceptives, progestogens, danazol, gonadotropin-releasing hormone agonists and anti-progestogens all have been employed for the treatment of endometriosis. • No clinical trials have compared directly medical vs surgical treatment of endometriosis; therefore, there is no substantial evidence to establish the superiority of one approach over the other. • Costs and side effects often dictate the choice of medical treatment. • In women with symptoms of pelvic pain, visible endometriosis observed during surgery should be treated. • Surgical treatment for endometriosis, followed by medical therapy, offers longer symptom relief compared to surgery alone. • Definitive treatment of endometriosis should be reserved for women with debilitating symptoms that can reasonably be attributed to the disease who have completed childbearing and have failed to respond to alternative treatments. • Further clinical trials designed to compare medical and surgical treatment are clearly warranted.
American Congress of Obstetricians and Gynecologists: **American Congress of Obstetricians and Gynecologists Practice Bulletin: Management of Endometriosis (2010)[24]** Reaffirmed 2018	• Transvaginal ultrasonography is the imaging modality of choice when assessing the presence of endometriosis. • Medical suppressive therapy improves pain symptoms; however, recurrence rates are high after the medication is discontinued. • After an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives (OCs)and non-steroidal anti-inflammatory drugs (NSAIDs), empiric therapy with a 3-month course of a gonadotropin-releasing hormone (GnRH) agonist is appropriate. • In patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or depot medroxyprogesterone acetate (DMPA) are effective compared with placebo and are equivalent to other more costly regimens. • GnRH agonists may have significant side effects, including hot flushes, vaginal dryness, and osteopenia. • Danazol has a side effect profile, which includes acne, hirsutism, and myalgias, that is more severe than other drugs available. • Long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea. • Hormone therapy with estrogen is not contraindicated after hysterectomy and bilateral salpingo-oophorectomy for endometriosis. • There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also a significant rate of pain recurrence. • Medical suppressive therapies such as OCs or GnRH agonists for endometriosis-associated infertility are ineffective.

Clinical Guideline	Recommendation(s)
	• Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear. • When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief.
Hereditary Angioedema International Working Group: **Evidence-Based Recommendations for the Therapeutic Management of Angioedema Owing to Hereditary C1 Inhibitor Deficiency (2012)**[25]	<u>Treatment of acute attacks</u> • All patients should have access to at least one of the specific medications, plasma-derived and recombinant C1 inhibitors, icatibant and ecallantide, even if still asymptomatic. • Whenever possible, patients should have the acute medication at home and be trained to self-administer these medications. • All attacks, regardless of location, should be treated as soon as they are recognized by the patients, ideally before the development of visible or disabling symptoms. • Report to the hospital immediately if laryngeal symptoms persist after an initial acute treatment. <u>Prophylactic treatment</u> • On-demand treatment for acute attacks should be the initial goal for all patients. Long-term prophylactic treatment is appropriate for patients in whom on-demand acute treatment was inadequate. • 17-α-alkylated androgens (e.g., danazol) can be considered in patients ≥16 years of age and women who are not pregnant or breastfeeding. Doses exceeding 200 mg/day are not recommended. • Plasma-derived C1inhibitors can be considered with individualized dosing to optimize clinical response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for androgens are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Androgens[1-18]

Indication	Danazol	Methyl-testosterone	Oxan-drolone	Testosterone (Buccal, Intranasal, Transdermal Patch, Gel and Nasal Gel)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Delayed puberty (males)		✔				✔ (IM)	
Hypogonadotropic hypogonadism (congenital or acquired in males)		✔		✔	✔	✔ (IM, SC)	✔
Metastatic mammary cancer (female)		✔				✔ (IM)	
Primary hypogonadism (congenital or acquired in males)		✔		✔	✔	✔ (IM, SC)	✔
Treatment of endometriosis amenable to hormonal management (female)	✔						
Treatment of fibrocystic breast disease (female)	✔						
Prevention of attacks of hereditary angioedema (males and females)	✔						
Adjunctive therapy to promote weight gain after weight loss following: extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight			✔				
To offset the protein catabolism associated with prolonged administration of corticosteroids			✔				
For the relief of the bone pain frequently accompanying osteoporosis			✔				

IM=intramuscular, SC-subcutaneous

IV. Pharmacokinetics

The pharmacokinetic parameters of the androgens are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Androgens[1]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Danazol	Well absorbed (% not reported)	Not reported	Liver	Renal (% not reported), fecal (% not reported)	9 to 23.7 hours
Methyltestosterone	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes
Oxandrolone	High (% not reported)	94 to 97	Not reported	Renal (60), feces (3)	5 to 13 hours
Testosterone	10 (gel)	98	Liver	Renal (90), fecal (6)	5.7 hours (buccal); 10 to 100 minutes (gel, patch); 70.8 days (implant)
Testosterone cypionate	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 days
Testosterone enanthate	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes
Testosterone undecanoate	Not reported	98	Liver	Renal (90), fecal (6)	10 to 100 minutes

V. Drug Interactions

Major drug interactions with the androgens are listed in Table 5.

Table 5. Major Drug Interactions with the Androgens[1]

Generic Name(s)	Interaction	Mechanism
Danazol, methyltestosterone, oxandrolone, testosterone	Warfarin	Androgens may decrease anticoagulant requirements. Monitor anticoagulant effects.
Danazol	Atorvastatin, fluvastatin, lovastatin, simvastatin	Severe myopathy or rhabdomyolysis may occur with coadministration of these drugs. When possible, consider avoiding this drug combination and administering alternative therapy.
Danazol, methyltestosterone, oxandrolone, testosterone	Bupropion	Concurrent use of systemic steroids and bupropion may result in lowering of the seizure threshold.
Testosterone	Paclitaxel	Concurrent use of paclitaxel and testosterone may result in increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the androgens are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Androgens[1-18]

Adverse Event	Danazol	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Central Nervous System									
Abnormal dreams	-	-	-	-	1.3 (gel)	-	-	-	-
Anxiety	-	✔	✔	✔	✔ (solution)	✔ (implant)	✔	✔	-
Asthenia	-	-	-	-	0 to 3 (gel)	-	-	-	-
Depression	-	✔	✔	✔	0 to 1 (gel); 3 (patch)	✔ (implant)	✔	✔	-
Dizziness	-	-	-	-	✔ (gel)	-	-	-	-
Emotional lability	✔	-	-	-	0 to 3 (gel); ✔ (solution)	-	-	-	✔ (injection)
Headache	-	✔	-	-	0 to 4.3 (gel); 4 (patch); 5 to 6 (solution)	✔ (implant) ≥3 (nasal)	✔	✔	✔ (injection) 4.8 (oral)
Insomnia	-	-	✔	✔	-	-	-	-	✔ (injection)
Libido, increased or decreased	-	✔	✔	✔	0 to 3 (gel)	✔ (implant)	✔	✔	-
Migraine	-	-	-	-	✔ (gel)	-	-	-	-
Nervousness	✔	-	-	-	0 to 3 (gel)	-	-	-	-
Paresthesia, generalized	-	✔	-	-	-	✔ (implant)	✔	✔	-
Dermatologic									
Acne	✔	✔	✔	✔	1 to 8 (gel); ✔ (solution)	✔ (implant)	✔	✔	5.2 (injection)
Allergic contact dermatitis	-	-	-	-	✔ (gel); 4 (patch)	-	-	-	-
Alopecia	-	-	-	-	0 to 1 (gel)	-	-	-	-
Application site edema	-	-	-	-	✔ (solution)	-	-	-	-
Application site erythema	-	-	-	-	✔ (gel); 7 (patch); 5 to 7 (solution)	-	-	-	-
Application site irritation	-	-	-	-	✔ (gel); 7 to 8 (solution)	-	-	-	-
Application site reaction	-	-	-	-	2 to 6 (gel)	✔ (implant)	-	-	-
Application site warmth	-	-	-	-	✔ (solution)	-	-	-	-
Burning at application site	-	-	-	-	3 (patch)	-	-	-	-
Burn-like blister reaction under system	-	-	-	-	12 (patch)	-	-	-	-

Adverse Event	Danazol	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Dry skin	-	-	-	-	2 (gel)	-	-	-	-
Folliculitis	-	-	-	-	✔ (solution)	-	-	-	-
Hair loss	✔	-	-	-	-	-	-	-	-
Hirsutism	✔	✔	✔	✔	-	✔ (implant)	✔	✔	-
Hyperhidrosis	-	-	-	-	-	-	-	-	✔ (injection)
Inflammation and pain at injection site	-	-	-	-	-	-	✔	✔	4.6 (injection)
Induration at application site	-	-	-	-	3 (patch)	-	-	-	-
Male pattern baldness	-	✔	✔	✔	-	-	✔	✔	-
Pruritus	-	-	-	-	2 (gel); 37 (patch)	-	-	-	-
Rash	-	-	-	-	2 (patch)	-	-	-	-
Seborrhea	✔	-	-	-	-	-	✔	-	-
Skin reactions	-	-	✔	✔	16 (gel)	-	-	-	-
Vesicles at application site	-	-	-	-	6 (patch)	-	-	-	-
Endocrine and Urogenital									
Amenorrhea	-	✔	-	-	-	-	-	✔	-
Benign prostatic hyperplasia	-	-	-	-	0 to 1 (gel)	-	-	-	-
Breast pain	-	-	-	-	1 to 3 (gel) ✔ (solution)	-	-	-	-
Erectile dysfunction	-	-	-	-	✔ (gel)	-	-	-	-
Estradiol increased	-	-	-	-	-	-	-	-	2.6 (injection)
Flushing	✔	-	-	-	-	-	-	-	-
Gynecomastia	-	✔	✔	✔	0 to 3 (gel)	✔ (implant)	✔	✔	-
Hot flushes	-	-	-	-	0 to 1 (gel)	-	-	-	-
Hypogonadism	-	-	-	-	-	-	-	-	2.6 (injection)
Inhibition of gonadotropin secretion	-	✔	✔	✔	-	-	-	✔	-
Menstrual disturbances	✔	✔	✔	✔	-	-	-	✔	-
Oligospermia	-	✔	✔	✔	-	-	✔	✔	-
Penile erections, excessive frequency and duration	-	✔	✔	✔	✔ (gel)	✔ (implant)	✔	✔	-
Prostate carcinoma	-	-	-	-	1 (gel)	-	-	-	✔ (injection)
Prostate disorder	-	-	-	-	3 to 5 (gel); 5 (patch)	-	-	-	-
Prostate enlarged	-	-	-	-	12 (gel)	-	-	-	-
Prostate specific antigen increased	-	-	-	-	0 to 11 (gel); 1 to 4 (solution)	≥3 (nasal)	-	-	4.6 (injection)

Adverse Event	Danazol	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Semen and sperm abnormalities	✔	-	✔	✔	✔	-	-	-	-
Spontaneous penile erection	-	-	✔	✔	0 to 1 (gel)	-	-	-	-
Sweating	✔	-	-	-	-	-	-	-	-
Testis disorder	-	-	-	-	0 to 3 (gel)	-	-	-	-
Urinary symptoms	-	-	-	-	4 (gel)	-	-	-	-
Vaginal dryness	✔	-	-	-	-	-	-	-	-
Virilization	-	✔	-	-	-	-	-	✔	-
Fluid and Electrolyte Disturbances									
Edema	✔	-	✔	✔	-	-	-	-	-
Retention of calcium, chloride, inorganic phosphates, potassium, sodium and water	-	✔	✔	✔	-	-	✔	✔	-
Gastrointestinal									
Abdominal symptoms	-	-	-	-	✔ (gel)	-	-	-	-
Alterations in liver function tests	-	✔	✔	✔	-	✔ (implant)	✔	✔	-
Cholestatic jaundice	-	✔	✔	✔	-	-	✔	✔	-
Diarrhea	-	-	-	-	3 to 4 (solution)	-	-	-	✔ (injection)
Gastrointestinal bleeding	-	-	-	-	2 (patch)	-	-	-	-
Nausea	-	✔	✔	✔	-	✔ (implant)	✔	✔	2.4 (oral)
Vomiting	-	-	✔	✔	3 to 4 (solution)	-	-	-	-
Hematologic									
Anemia	-	-	-	-	3 (gel)	-	-	-	-
Hematocrit/ hemoglobin increased	-	-	✔	✔	0 to 3 (gel); 4 to 7 (solution)	-	-	-	✔ (injection) 4.8 (oral)
Suppression of clotting factors II, V, VII and X	-	✔	-	-	-	✔ (implant)	✔	✔	-
Polycythemia	-	✔	-	-	✔ (gel)	✔ (implant)	✔	✔	-
Metabolic									
Blood glucose increased	-	-	✔	✔	✔ (solution)	-	-	-	3.6 (oral)
Cholesterol, increased	-	✔	-	-	-	✔ (implant)	✔	✔	-
High density lipoprotein, decreased	-	-	-	-	-	-	-	-	3.0 (oral)
Weight gain	✔	-	-	-	-	-	-	-	✔ (injection)
Other									
Blood pressure increased	-	-	-	-	✔ (solution)	✔ (nasal)	-	-	✔ (injection)
Bronchotis	-	-	-	-	3.8 to 4.3 (nasal gel)	-	-	-	-
Epistaxis	-	-	-	-	3.8 to 4.3 (nasal gel)	≥3 (nasal)	-	-	-

Adverse Event	Danazol	Methyl-testosterone	Oxan-drolone	Oxyme-tholone	Testosterone (Topical)	Testosterone (Other Formulations)	Testosterone Cypionate	Testosterone Enanthate	Testosterone Undecanoate
Fatigue	-	-	-	-	✔ (gel)	-	-	-	✔ (injection)
Hypersensitivity	-	-	-	-	-	-	✔	-	-
Hypertension	-	-	-	-	0 to 3 (gel)	-	-	-	-
Influenza-like illness/malaise	-	-	-	-	✔ (gel)	-	-	-	-
Laboratory test abnormality	-	-	-	-	3 to 9 (gel)	✔ (implant)	-	-	-
Lacrimation increased	-	-	-	-	✔ (solution)	-	-	-	-
Nasal discomfort	-	-	-	-	3.8 to 5.8 (nasal gel)	-	-	-	-
Nasal scab	-	-	-	-	3.8 to 5.8 (nasal gel)	-	-	-	-
Nasopharyngitis	-	-	-	-	✔ (solution) 3.8 to 8.7 (nasal gel)	≥3 (nasal)	-	-	✔ (injection)
Pain in extremities	-	-	-	-	✔ (gel) 4.3 (nasal gel)	-	-	-	-
Procedural pain	-	-	-	-	4.3 (nasal gel)	-	-	-	-
Parosmia	-	-	-	-	5.8 (nasal gel)	-	-	-	-
Rhinorrhea	-	-	-	-	3.8 to 7.2 (nasal gel)	≥3 (nasal)	-	-	-
Sinusitis	-	-	-	-	3.8 (nasal gel)	-	-	-	-
Upper respiratory tract infection	-	-	-	-	3.8 to 4.3 (nasal gel)	-	-	-	-
Vitreous detachment	-	-	-	-	✔ (gel)	-	-	-	-
Voice change	✔	-	✔	✔	-	-	-	-	-

✔ Incidence not specified.
-Event not reported or incidence <1%.

Table 7. Boxed Warning for Danazol[18]

WARNING
Use of danazol in pregnancy is contraindicated. A sensitive test (e.g., beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally, a nonhormonal method of contraception should be used during therapy. If a patient becomes pregnant while taking danazol, discontinue administration of the drug and apprise the patient of the potential risk to the fetus. Thromboembolism, thrombotic and thrombophlebitic events, including sagittal sinus thrombosis and life-threatening or fatal strokes have been reported. Experience with long-term therapy with danazol is limited. Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intra-abdominal hemorrhage. Therefore, alert the physician to this possibility. Attempts should be made to determine the lowest dose that will provide adequate protection. If danazol was begun at a time of exacerbation of hereditary angioneurotic edema due to trauma, stress or other cause, periodic attempts to decrease or withdraw therapy should be considered. Danazol has been associated with several cases of benign intracranial hypertension also known as pseudotumor cerebri. Early signs and symptoms of benign intracranial hypertension include papilledema, headache, nausea and vomiting, and visual disturbances. Screen patients with these symptoms for papilledema and, if present, advise the patients to discontinue danazol immediately and refer them to a neurologist for further diagnosis and care.

Table 8. Boxed Warning for Oxandralone[18]

WARNING
Peliosis hepatis: Peliosis hepatis, a condition in which liver and, sometimes, splenic tissue is replaced with blood-filled cysts, has occurred in patients receiving androgenic anabolic steroids. These cysts are sometimes present with minimal hepatic dysfunction and have been associated with liver failure. Often, they are not recognized until life-threatening liver failure or intra-abdominal hemorrhage develops. Withdrawal of drug usually results in complete disappearance of lesions. Liver cell tumors: Most often these tumors are benign and androgen-dependent, but fatal malignant tumors have occurred. Withdrawal of drug often results in regression or cessation of tumor progression. However, hepatic tumors associated with androgens or anabolic steroids are much more vascular than other hepatic tumors and may be silent until life-threatening, intra-abdominal hemorrhage develops. Blood lipid changes: Blood lipid changes associated with increased risk of atherosclerosis are seen in patients treated with androgens and anabolic steroids. These changes include decreased high-density lipoprotein (HDL) and, sometimes, increased low-density lipoprotein (LDL). The changes may be very marked and could have a serious impact on the risk of atherosclerosis and coronary artery disease.

Table 9. Boxed Warning for Transdermal Testosterone[18]

WARNING
Virilization has been reported in children who were secondarily exposed to transdermal testosterone. Ensure that children avoid contact with unwashed or unclothed application sites in men using transdermal testosterone. Advise patients to strictly adhere to recommended instructions for use.

Table 10. Boxed Warning for Subcutaneous Testosterone Enanthate[18]

WARNING
Subcutaneous testosterone enanthate can cause blood pressure increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal MI, non-fatal stroke, and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease. Before initiating, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled. Starting approximately six weeks after initiating therapy, periodically monitor for and treat new-onset hypertension or exacerbations of preexisting hypertension and re-evaluate whether the benefits of testosterone

injection outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment. Due to this risk, use subcutaneous testosterone enanthate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

Table 11. Boxed Warning for Testosterone Undecanoate[18]

WARNING
• Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. • Following each injection of testosterone undecanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis. • Because of the risks of serious POME reactions and anaphylaxis, testosterone undecanoate is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed REMS Program. • Testosterone undecanoate can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease • Before initiating testosterone undecanoate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled. Starting approximately 3 weeks after initiating therapy or changing the dose, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone undecanoate. Re-evaluate whether the benefits of testosterone undecanoate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment. • Due to this risk, use testosterone undecanoate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

VII. Dosing and Administration

The usual dosing regimens for the androgens are listed in Table 12.

Table 12. Usual Dosing Regimens for the Androgens[1-18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Danazol	Treatment of endometriosis amenable to hormonal management (female): Capsule: initial, 200 to 800 mg in two divided doses; continue therapy uninterrupted for three to six months (up to nine months) Treatment of fibrocystic breast disease (females): Capsule: initial, 100 to 400 mg in two divided doses Prevention of attacks of hereditary angioedema of all types (males and females): Capsule: initial, 200 mg given two to three times a day; after a favorable	Safety and effectiveness in pediatric patients have not been established.	Capsule: 50 mg 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	response, decrease dose by 50% or less at intervals of one to three months or longer depending on the frequency of attacks; if an attack occurs, increase dose by up to 200 mg/day		
Methyltestosterone (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Capsule, tablet: 10 to 50 mg/day Metastatic mammary cancer (females): Capsule, tablet: 50 to 200 mg/day	Delayed puberty (males): Capsule, tablet: 10 to 50 mg/day for a limited duration (e.g., four to six months) Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation.	Capsule: 10 mg Tablet: 10 mg
Oxandrolone (CIII)	Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis: Tablet: 2.5 to 20 mg given in two to four divided doses for two to four weeks; this may be repeated intermittently as indicated	Adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis: Tablet: ≤0.1 mg/kg body weight or ≤0.045 mg/lb of body weight; repeated intermittently as indicated	Tablet: 2.5 mg 10 mg
Testosterone (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Testopel®: Pellets: 150 to 450 mg subcutaneous implantation every 3 to 6 months Testim® 1% and AndroGel® 1%: Topical gel: initial, 5 g applied once daily (preferably in the morning); maintenance, 5 to 10 g/day; maximum, 10 g/day AndroGel® 1.62%: Topical gel: initial, 40.5 mg applied	Safety and effectiveness in pediatric male patients below the age of 18 have not yet been established.	Implant (Testopel® pellets) 75 mg Topical gel: AndroGel® 1%: Metered-dose pumps: 1.25 g per pump (12.5 mg of testosterone) Unit-dose packets: 1.25 g (20.25 mg of testosterone) 2.5 g (25 mg of testosterone)

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	once daily (preferably in the morning); maintenance, 20.25 to 81 mg/day; maximum, 10 g/day Fortesta®: Topical gel: initial, 40 mg applied once daily (preferably in the morning); maintenance, 10 to 70 mg/day; maximum, 70 mg/day Natesto®: Nasal gel: 11 mg (2 pump actuations; 1 actuation per nostril) intranasally three times daily for total daily dose of 33 mg Topical solution: initial, 60 mg applied once daily in the morning; maintenance, 30 to 120 mg once daily; maximum, 120 mg daily Transdermal system: initial, 4 mg/day patch applied once nightly; maintenance, 2 to 6 mg/day applied at night		2.5 g (40.5 mg of testosterone) 5 g (50 mg of testosterone) AndroGel® 1.62%: Metered-dose pumps: 1.25 g per pump (20.25 mg of testosterone) Fortesta®: Metered-dose pumps: 0.5 g per pump (10 mg of testosterone) Testim® 1%: Unit-dose tubes: 5 g per tube (50 mg of testosterone) Natesto®: Metered-dose pump: 5.5 mg per pump Topical solution (metered-dose pumps, Axiron®): 90 mL per pump (30 mg of testosterone) Transdermal system (Androderm®): 2 mg/day 4 mg/day
Testosterone cypionate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection: 50 to 400 mg intramuscularly every two to four weeks	Safety and effectiveness in pediatric patients below the age of 12 years have not been established.	Injectable solution (vial): 100 mg/mL
Testosterone enanthate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection (IM): 50 to 400 mg intramuscularly every two to four weeks Injection (SQ): 75 mg subcutaneously once weekly; usual	Delayed puberty: Injection (IM): 50 to 200 mg intramuscularly every two to four weeks for a limited duration (e.g., four to six months) Androgen therapy should be used very cautiously in children and only by	Injectable solution (IM): 200 mg/mL Injectable solution (SQ, auto-injector): 50 mg/ 0.5 mL 75 mg/ 0.5 mL 100 mg/ 0.5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dosage range, 50 to 100 mg/week subcutaneously Metastatic mammary cancer (females): Injection (IM): 200 to 400 mg intramuscularly every two to four weeks	specialists who are aware of the adverse effects on bone maturation.	
Testosterone undecanoate (CIII)	Hypogonadotropic hypogonadism (congenital or acquired in males) and primary hypogonadism (congenital or acquired in males): Injection: 750 mg intramuscularly at initiation, at four weeks, and every 10 weeks thereafter Oral: initial, 237 mg twice daily; minimum, 158 mg twice daily; maximum, 396 mg twice daily	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.	Injectable oil: 750 mg/ 3 mL Capsules: 158 mg 198 mg 237 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the androgens are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Androgens

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Male Hypogonadism				
Morales et al.[26] (1994) Methyltestosterone (dose not reported)	OL Hypogonadal men with impotence associated with low total serum androgen levels (age not reported)	N=22 1 month	Primary: Recovery of sexual function; changes in levels of energy, mood or feeling of well being Secondary: Not reported	Primary: Only 9% of the patients reported a complete recovery of sexual function. The positive responses were recorded in men with the most profound testosterone deficiency. Visual analogue scales did not reveal noticeable changes for any individual in the levels of energy, mood or feeling of wellbeing between pretreatment and post-treatment assessments. The authors concluded that exogenous administration of androgens to impotent men should be limited to those with profound hypogonadism as documented by at least two abnormal serum free testosterone determinations. Secondary: Not reported
Kaufman et al.[27] (2011) Testosterone 1.62% (AndroGel) 2.5 g once daily vs placebo Doses were titrated up or down in 1.25 g increments to between 1.25 g	DB, MC, PC, RCT Hypogonadal men 18 to 80 years of age who were otherwise healthy, naïve to androgen replacement therapy or undergone appropriate washout period, had a serum testosterone <300, and BMI ≥18	N=274 182 days	Primary: Percentage of patients achieving serum total testosterone average concentrations within normal range of 300 to 1,000 ng/dL Secondary: Percentage of patients with maximum testosterone serum	Primary: The testosterone treatment group met the success criterion of ≥75% of patients achieving testosterone levels within the normal range on all time points with the exception of day 14. There were significantly more patients in the testosterone group compared to placebo achieving total testosterone average concentrations within normal range at 14, 56, 112, and 182 days (P<0.0001 for all comparisons). Secondary: For patients in the testosterone group, 88.8 to 97.3% had maximum testosterone concentrations ≤1,500 ng/dL, 0.5 to 4.5% between 1,800 and 2,500 ng/dL and 0.5 to 5.6% >2,500 dL compared to ≥96% had maximum testosterone concentrations ≤1,500 ng/dL. Estradiol concentrations were within the normal range of 10 to 40 ng/mL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily and 5.0 g daily until day 42 at which time the doses were not changed.	kg/m^2 to ≤40 kg/m^2		concentrations in the ranges ≤1,500 ng/dL, between 1,800 and 2,500 ng/dL and >2,500 dL; and measurements of SHBG, LH, FSH, serum inflammatory and cardiovascular risk factors, waist-to-hip ratio, and serum markers of bone metabolism	for the testosterone-treated patients, except for day 56 with patients treated with 1.25 g which was above the upper limit of normal. At day 84, there was a significant decrease in sex hormone binding globulin from baseline (P=0.0012) but was not significant on day 182. When compared to placebo, this difference was statistically significant on day 84 (P=0.0193). There were significant decreases in LH and FSH on days 84 and 182 (P<0.0001) in the testosterone group; however, there was no significant difference in the placebo group. There were significant decreases of IL-10 on days 84 (P<0.0001) and 182 (P=0.0132) in the testosterone groups. When compared to the placebo group, the difference was statistically significant (P=0.0254) on day 84. There were no significant changes in other inflammatory cytokines. There was a significant increase in serum marker of bone formation (serum bone-specific alkaline phosphatase) at day 182 (P<0.0001); however, this was not significantly different from placebo. There was a significant decrease in serum marker of bone resorption (serum type-I cross-linked C telopeptide) at days 84 and 182 (P<0.001); however, only day 84 was significantly different from placebo (P<0.05). Serious treatment-emergent adverse effects were 2.1% in testosterone treated patients and 2.5% in placebo. In the testosterone groups, 55.6% of patients experienced at least on treatment-emergent adverse effect compared to 37.5% in the placebo group.
Snyder et al.[28] (2016) Testosterone 1% (AndroGel) 5 g once daily vs	DB, MC, PC, RCT Men ≥65 years of age with subjective and objective evidence of impaired sexual or physical function or reduced vitality	N=790 12 months	*Sexual function trial*: Primary: Change from baseline in the score for sexual activity on the Psychosexual Daily Questionnaire	*Sexual function trial*: Primary: Sexual activity increased more with testosterone treatment than with placebo (treatment effect [the mean difference in the change from baseline between participants assigned to testosterone and those assigned to placebo], 0.58; P<0.001). Secondary: Testosterone treatment was associated with increased sexual desire

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo The dose of testosterone gel was adjusted after each measurement to attempt to keep the concentration within the normal range for young men	and a serum testosterone concentration on 2 morning specimens that averaged <275 ng/dL *Sexual function trial*: self-reported decreased libido, score <20 on sexual-desire domain, partner willing to have intercourse *Physical function trial*: self-reported difficulty walking or climbing stairs and a gait speed of less than 1.2 m per second on the 6-minute walk test *Vitality trial*: self-reported low vitality, score <40 on the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale		Secondary: Changes in the score on the erectile-function domain (range, 0 to 30, with higher scores indicating better function) of the International Index of Erectile Function (IIEF) and the sexual-desire domain of the DISF-M-II *Physical function trial*: Primary: Percentage of men who increased the distance walked in the 6-minute walk test by at least 50 m Secondary: Percentage of men whose score on the physical-function domain (PF-10; range, 0 to 100, with higher scores indicating better function) of the SF-36 increased by at least 8 points, and changes from baseline in the 6-	according to the DISF-M-II (treatment effect, 2.93; P<0.001) and increased erectile function according to the IIEF (treatment effect, 2.64; P<0.001). Men in the testosterone group were more likely than those in the placebo group to report that their sexual desire had improved since the beginning of the trial (P<0.001). *Physical function trial*: Primary: There were no significant differences between the testosterone group and the placebo group in the percentage of men whose 6-minute walking distance increased by at least 50 m (OR, 1.42; P=0.20). Secondary: There were no significant differences between the testosterone group and the placebo group in the change from baseline in the six-minute walking distance (mean difference, 4.09 m; P=0.28), or the percentage of men whose PF-10 score increased by at least eight points (OR, 1.34; P=0.15). There was a significant between-group difference in the change from baseline in the PF-10 score (mean difference, 2.75 points; P=0.03). *Vitality trial*: Primary: Testosterone treatment showed no significant benefit over placebo with respect to vitality, as determined by an increase of at least four points in the FACIT–Fatigue score (OR, 1.23; P=0.30). Secondary: There appeared to be a small effect on the change from baseline in the FACIT–Fatigue score that did not reach significance (mean difference, 1.21 points; P=0.06). there were significant differences between the testosterone group and the placebo group in the SF-36 vitality score (mean difference, 2.41 points; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			minute walking distance and PF-10 score *Vitality trial*: Primary: percentage of men whose score on the FACIT–Fatigue scale increased by at least 4 points Secondary: Change from baseline in the FACIT–Fatigue, the score on the vitality scale (range, 0 to 100, with higher scores indicating more vitality) of the SF-36	
Snyder et al.[29] (2017) Testosterone 1% (AndroGel) 5 g once daily vs placebo The dose of testosterone gel was adjusted after each measurement to	DB, MC, PC, RCT Men ≥65 years of age with subjective and objective evidence of impaired sexual or physical function or reduced vitality and a serum testosterone concentration on two morning specimens that averaged <275	N=211 12 months	Primary: Percent change from baseline in vBMD of trabecular bone in the lumbar spine Secondary: vBMD of peripheral bone and whole bone of the lumbar spine and trabecular, peripheral, and whole bone of the hip; estimated	Primary: Testosterone treatment increased mean lumbar spine trabecular vBMD (primary outcome) by 7.5% (95% CI, 4.8 to 10.3%), compared with 0.8% (95% CI, −1.9 to 3.4%) by placebo, a difference of 6.8% (95% CI, 4.8 to 8.7%; P<0.001). Secondary: Testosterone treatment increased peripheral and whole-bone vBMD of the spine and trabecular, peripheral, and whole-bone vBMD of the hip. The magnitudes of the increases were less in the hip than in the spine but still statistically significant. Testosterone treatment increased estimated strength of spine trabecular bone by 10.8% (95% CI, 7.4 to 14.3%), compared with 2.4% (95% CI, −1.0 to 5.7%) in placebo-treated men. The difference was 8.5% (95% CI, 6.0 to 10.9%; P<0.001). Testosterone treatment also significantly increased estimated strength of peripheral and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
attempt to keep the concentration within the normal range for young men	ng/dL		strength of the same sites by finite element analysis	whole bone.
Snyder et al.[30] (2017) Testosterone 1% (AndroGel) 5 g once daily vs placebo The dose of testosterone gel was adjusted after each measurement to attempt to keep the concentration within the normal range for young men	DB, MC, PC, RCT Men ≥65 years of age with subjective and objective evidence of impaired sexual or physical function or reduced vitality, a serum testosterone concentration on two morning specimens that averaged <275 ng/dL, and baseline hemoglobin levels ≥10 and <12.7 g/dL	N=126 (n=62 with unexplained anemia) 12 months	Primary: Dichotomous change in hemoglobin in the men with unexplained anemia (a change of ≥1.0 g/dL for the dichotomous outcomes was selected) Secondary: Continuous change in hemoglobin in the men with unexplained anemia	Primary: At month 12, 54% of testosterone-treated men but only 15% of placebo-treated men had experienced increases of 1.0 g/dL or more above baseline (adjusted OR, 31.5; 95% CI, 3.7 to 277.8; P=0.002). Secondary: Testosterone increased hemoglobin concentrations by continuous analysis in men with unexplained anemia (adjusted mean difference, 0.83 g/dL; 95% CI, 0.48 to 1.39; P<0.001), men with known causes of anemia (adjusted mean difference, 0.64 g/dL; 95% CI, 0.12 to 1.17; P=0.02), and nonanemic men (adjusted mean difference, 0.90 g/dL; 95% CI, 0.78 to 1.03; P<0.001). The effect of testosterone on continuous change in hemoglobin levels did not differ by anemia classification (P=0.43). At month 12, 12 of 24 (58.3%) testosterone-treated men with unexplained anemia at baseline were no longer anemic, compared with six of 24 (22.2%) placebo-treated men (OR, 17.0; 95% CI, 2.8 to 104.0; P=0.002).
Budoff et al.[31] (2017) Testosterone 1% (AndroGel) 5 g once daily vs placebo The dose of testosterone gel was	DB, MC, PC, RCT Men ≥65 years of age with subjective and objective evidence of impaired sexual or physical function or reduced vitality, and a serum testosterone concentration on two morning	N=138 12 months	Primary: Noncalcified coronary artery plaque volume Secondary: Total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with	Primary: For the primary outcome, testosterone treatment was associated with a significantly greater increase from baseline to month 12 (from median of 204 mm^3 to 232 mm^3; change: mean, 40 mm^3; 95% CI, 23 to 56 mm^3) than placebo (from median of 317 mm^3 to 325 mm^3; change: mean, 4 mm^3; 95% CI, −14 to 22 mm^3) (estimated difference, 41 mm^3; 95% CI, 14 to 67 mm^3; P=0.003). Secondary: For the secondary outcome of total plaque volume, testosterone was significantly associated with a greater increase from baseline to month 12 (from a median of 272 mm^3 to 318 mm^3; change: mean, 57 mm^3; 95% CI, 35 to 78 mm^3) than placebo (from a median of 499 mm^3 to 541 mm^3;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
adjusted after each measurement to attempt to keep the concentration within the normal range for young men	specimens that averaged <275 ng/dL		higher values indicating more severe atherosclerosis)	change: mean, 21 mm^3; 95% CI, 0 to 42 mm^3) (estimated difference, 47 mm^3; 95% CI, 13 to 80 mm^3; P=0.006). For the secondary outcome of coronary artery calcium score, testosterone was not statistically significantly associated with a change from baseline to 12 months (change in testosterone group: mean, 53 Agatston units; 95% CI, 25 to 82 Agatston units; change in placebo group: mean, 118 Agatston units; 95% CI, 73 to 164 Agatston units). The median scores changed from 255 to 244 Agatston units in the testosterone group vs 494 to 503 Agatston units in the placebo group (estimated difference, −27 Agatston units; 95% CI, −80 to 26 Agatston units; P=0.31).
Resnick et al.[32] (2017) Testosterone 1% (AndroGel) 5 g once daily vs placebo The dose of testosterone gel was adjusted after each measurement to attempt to keep the concentration within the normal range for young men	DB, MC, PC, RCT Men ≥65 years of age with subjective and objective evidence of impaired sexual or physical function or reduced vitality, a serum testosterone concentration on two morning specimens that averaged <275 ng/dL, and age-associated memory impairment based on baseline subjective memory complaints and objective memory performance	N=439 12 months	Primary: Mean change from baseline to six months and 12 months for delayed paragraph recall (score range, 0 to 50) Secondary: Mean changes in visual memory (Benton Visual Retention Test; score range, 0 to −26), executive function (Trail-Making Test B minus A; range, −290 to 290), and spatial ability (Card Rotation Test; score range, −80 to 80)	Primary: Testosterone treatment compared with placebo was not associated with significant differences in the mean change from baseline to month six and to month 12 in delayed paragraph recall (adjusted estimated difference, −0.07; 95% CI, −0.92 to 0.79; P=0.88). Secondary: There was no significant association between testosterone treatment and mean change from baseline to month six and month 12 in visual memory (adjusted estimated difference, −0.28; 95% CI, −0.76 to 0.19; P=0.24), executive function (adjusted estimated difference, −5.51; 95% CI, −12.91 to 1.88; P=0.14), or spatial ability (adjusted estimated difference, −0.12; 95% CI, −1.89 to 1.65; P=0.89).
Kaufman et al.[33] (2012) Testosterone 1.62%	OL, ES (Kaufman [2011]) Hypogonadal men	N=191 1 year	Primary: Percentage of patients achieving serum total	Primary: On day 364, 77.9% (95% CI, 70.0 to 84.6%) of patients continuing on testosterone treatment achieved testosterone levels within the normal range which met the success criterion of ≥75% of patients achieving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(AndroGel) 1.25 to 5.00 g once daily Doses were titrated up or down in 1.25 g increments on days 182, 96, 210 and 266 to between 1.25 g daily and 5.0 g.	18 to 80 years of age who were otherwise healthy, naïve to androgen replacement therapy or undergone appropriate washout period, had a serum testosterone <300, and BMI ≥18 kg/m2 to ≤40 kg/m2		testosterone average concentrations within normal range of 300 to 1,000 ng/dL Secondary: Percentage of patients with maximum testosterone serum concentrations in the ranges ≤1,500 ng/dL, between 1,800 and 2,500 ng/dL and >2,500 dL; and measurements of SHBG, LH, FSH, serum inflammatory and cardiovascular risk factors, waist-to-hip ratio, and serum markers of bone metabolism	testosterone levels within the normal range. The patient continuing on testosterone also achieved the success criterion on day 266; however, the group previously treated with placebo only reached the criterion on day 264. Secondary: For all patients, 93.5% had maximum testosterone serum concentrations ≤1,500 ng/dL, 3.4% were between 1,800 and 2,500 ng/dL and no patients were >2,500 dL. Mean dihydrotestosterone levels were in the eugonadal reference range (11.2 to 95.5 ng/dL) except for the formerly placebo treated 3.75g treated patients. Mean estradiol levels were in the normal range (10 to 40 pg/dL). There was a significant increase in SHBG from baseline on days 266 (P<0.0001) and 364 (P<0.0166) in the continuing treatment group. There were significant decreases in luteinizing hormone from baseline on days 266 and 364 for the continuing active treatment group (P<0.0001 for both days) and the formerly placebo treated group (P<0.0054 and P=0.0309, respectively). There were significant decreases in FSH from baseline on days 266 and 364 for the continuing active treatment group (P<0.0001 for both days) and the formerly placebo treated group (P<0.0001 and P<0.0087, respectively). There were significant decreases of interleukin-10 on day 364 in the continuing active treatment group (P<0.001) and day 266 in the formerly placebo treated group (P<0.0089). The matrix metalloprotease-9 levels decreases significantly from baseline on days 266 (P<0.0080) and 364 (P<0.0055) in the continuing active treatment group, but not he formerly placebo group. There was a significant increase in serum bone-specific alkaline phosphatase on day 264 (P<0.0001), but on day 364. There was a significant decrease in serum type-I cross-linked C telopeptide on days 266 and 364 (P<0.001) for the continuing active treatment group, but not the formerly placebo group. The most common treatment-emergent adverse effect leading to discontinuation was an increase in prostate specific antigen levels (5.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were 79 (41.4%) patients that experienced at least one treatment-emergent adverse effect. The most common treatment-emergent adverse effects were increased prostate specific antigen, upper respiratory tract infection, nasopharyngitis, hypertension, influenza, sinusitis and acne.
Pexman-Fieth et al.[34] (2014) ESPRIT Testosterone 1% (AndroGel) 50 to 100 mg once daily	OL, OS Hypogonadal men ≥ 18 years of age who were otherwise healthy, naïve to testosterone therapy	N=712 6 months	Primary: Effect of treatment on hypogonadal symptoms and quality of life as assessed by Aging Males' Symptoms (AMS) scale Secondary: Erectile dysfunction (International Index of Erectile Function [IIEF]), fatigue (Multidimensional Fatigue Inventory [MFI]), and surrogates for body composition (waist circumference, body mass index [BMI])	Primary: In both the responder (patients with one or more documented total testosterone level within the normal range while receiving treatment) and nonresponder (patients with no documented total testosterone level within the normal range while receiving treatment) groups, the AMS score decreased significantly. Secondary: In both responders and nonresponders, mean total IIEF scores increased significantly (P<0.0001 in both) over six months. The mean MFI total score decreased significantly in both responders and nonresponders (P<0.0001 for both). Mean BMI decreased significantly (P<0.0001) in responders but remained stable in nonresponders. In both responders and nonresponders, the mean waist circumference decreased significantly from baseline and the decrease became significant at three months (P<0.0001).
Dobs et al.[35] (2004) Testosterone buccal (Striant®) 30 mg two times a day vs testosterone 1% gel (AndroGel®) 50 mg daily	OL, PG, RCT Men 18 to 80 years of age with testosterone deficiency with serum testosterone <8.7 mmol/L (2.5 ng/mL) and BMI <35 kg/m^2	N=25 14 days	Primary: Percentage of patients who achieved average serum testosterone within normal range 3.0 to 10.5 ng/mL Secondary: Average, maximum and minimum serum testosterone, time to	Primary: Twelve of 13 (92.3%) patients using testosterone buccal and 10 of 12 (83.3%) patients using testosterone gel achieved average 24-hour serum testosterone within normal range (P value not reported). Secondary: All pharmacokinetic parameters were similar between the two groups. In the testosterone buccal and testosterone gel groups, the average serum testosterone was 4.8±1.4 and 4.4±1.4 ng/mL, maximum concentration was 8.5±3.3 and 7.5±3.5 ng/mL, minimum concentration was 2.5±0.8 and 2.5±0.9 ng/mL, time to maximum concentration was 13.4±9.9 and 13.6±7.9 ng/mL and time to minimum concentration was 7.9±7.4 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			maximum and minimum serum testosterone and percentage of time that serum testosterone was within the normal range	9.3±6.6 ng/mL, respectively (P>0.05 for all). During a 24-hour period, 83.4 and 75.3% of patients in the buccal and gel groups, respectively, had a serum testosterone within the normal range (P>0.05).
Korbonits et al.[36] (2004) Testosterone buccal (Striant®) 30 mg two times a day vs testosterone patch (Andropatch®‡ or Androderm® TD) 5 mg once daily	MC, RCT Men with testosterone deficiency with a morning serum testosterone <6.94 nmol/L, normal age-related PSA levels and Hct <50	N=66 7 days	Primary: Non-inferiority analysis (endpoints not defined) Secondary: Efficacy analysis of superiority (endpoints not defined)	Primary: Investigators concluded that non-inferiority was established (results not reported). Secondary: In the buccal testosterone group, the mean testosterone concentrations at all measured time points (days three, four, six, seven and eight) were within the physiological range; whereas mean concentrations at five time points were outside of the physiological range among patients in the testosterone patch group. For both mean (0 to24 hour) and minimum testosterone levels, the proportion of patients with levels outside the physiological range was lower in the buccal group than in the patch group (the differences; P<0.001 for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch (mean AUC±SD; 451.31±140.71 h*nmol/L vs 304.63±134.46 h*nmol/L; 95% CI, 1.25 to 1.91; P<0.00001). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group. Comparatively, the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group; however, the mean minimum 24-hour testosterone level was below the physiological range. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Testosterone concentrations were within the physiological range in the buccal group for a significantly greater portion of the 24-hour treatment period compared to the patch group (84.9 vs 54.9%; P<0.001). Mean DHT levels were within the normal range (1.03 to 2.92 nmol/L) for both the buccal group (2.36±0.99 nmol/L) and the patch group (1.2±0.57 nmol/L). The median E2 concentrations increased from baseline to day seven, but returned to baseline levels at the follow-up visit. The median increase from baseline to day seven was greater in the buccal group (55.07 pmol/liter) compared to the patch group (34.87 pmol/L; P<0.001). A total of 51.5% of patients in the buccal group reported an adverse event compared to 47.1% in the patch group. The most commonly reported adverse events among both groups were application site disorders.
Swerdloff et al.[37] (2000) Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg 2 patches daily At 60 days, men	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Serum testosterone and free testosterone levels at 0, one, 30, 90 and 180 days; safety; serum DHT, E_2, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days Secondary: Not reported	Primary: At 30 and 90 days, testosterone gel 100 mg produced significantly higher average concentration testosterone levels over testosterone 50 mg and testosterone patch (27.46±1.12 vs 19.17±1.06 and 14.46±0.68 nmol/L, respectively; P=0.0001). At 180 days, serum testosterone levels and pharmacokinetics parameters were similar to those on days 30 and 90 in those patients who continued their initial randomized treatment. Patients switched to testosterone gel 75 mg had an average concentration testosterone level of 20.84±1.76 nmol/L at 180 days. This value was between the 180 day average concentration testosterone levels achieved with testosterone gel 50 mg (19.24±1.18) and testosterone gel 100 mg (24.72±1.05). Pharmacokinetics parameters of serum free testosterone levels on days one, 30, 90 and 180 mirrored those of serum testosterone levels. The free testosterone levels in the testosterone gel 100 mg group was 1.4- and 1.7-fold higher than the testosterone gel 50 mg and testosterone patch groups (P=0.001). The discontinuation rate at 90 days for the testosterone patch (27.6%) was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with serum testosterone levels <10.4 nmol/L who were applying AndroGel® 50 mg and men with serum testosterone levels >34.7 nmol/L who were applying AndroGel® 100 mg were instructed to apply AndroGel® 75 mg once daily for days 91 through 180.				significantly higher than testosterone gel 50 and 100 mg (8.2 and 6.4%, respectively; P=0.0002). Most patients discontinued treatment due to adverse skin reactions. Throughout the 180 days, increases in serum DHT levels were significant with testosterone gel 50 and 100 mg over the testosterone patch (P=0.0001). Mean serum increases to stable levels of E_2 occurred in 9.2, 30.9 and 45.5% of patients in the testosterone patch, testosterone gel 50 and testosterone gel 100 mg groups, respectively (P=0.001). All three treatment groups showed a small decrease in serum SHBG levels (P=0.0046). The mean percent suppression of serum LH levels was the smallest with testosterone patch (30 to 40%), intermediate with testosterone gel 50 mg (55 to 60%) and greatest with testosterone gel 100 mg (80 to 85%; P<0.01). The suppression of serum FSH paralleled that of serum LH levels. Secondary: Not reported
Wang et al.[38] (2000) Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs testosterone patch	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Mean change from baseline in serum testosterone concentrations, body composition and muscle strength at 90 and 180 days; mean change from baseline in sexual function and mood at 30, 60, 90, 120, 150 and 180 days; degree of skin irritation; mean change from	Primary: On day 90 the average serum testosterone concentration with testosterone gel 100 mg (27.46±1.12 nmol/L) was 1.4-fold higher than testosterone gel 50 mg (19.17±1.06 nmol/L) and 1.9-fold higher than the testosterone patch (14.46±0.68 nmol/L; P value not reported). On day 180 average serum testosterone concentrations for the treatment groups were 24.72±1.05, 19.24±1.18 and 14.14±0.88 nmol/L, respectively. The percent body fat and fat mass decreased in all treatment groups but was only significant with testosterone gel. At 90 days the total fat mass was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (P=0.0065 and P=0.0001, respectively). At 180 days the total fat mass decreased further with testosterone gel 100 mg (P=0.008). At 90 days, the percent body fat was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (P=0.0018 and P=0.001) and remained significant at 180 days.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Androderm®) 2.5 mg two patches daily At 90 days, dose adjustments were made in the AndroGel® groups based on the pre-application serum testosterone levels on day 60. Twenty subjects in the AndroGel® 50 mg group had their dose increased to 75 mg and 20 subjects in the AndroGel® 100 mg group had their dose reduced to 75 mg.			baseline in serum PSA levels at 30 and 90 days; mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries Secondary: Not reported	Significant increases in arm and leg muscle strength were seen in all three treatment groups without intergroup differences on days 90 and 180 (P values compared to baseline ranged between 0.0001 and 0.08). All subjects, regardless of treatment group, showed significant improvement in sexual motivation (P=0.0001), sexual desire (P=0.0001), sexual performance (P=0.0001), self-assessment of satisfaction of erection (P=0.0001) and percentage of full erection (P=0.0001). All three treatment groups showed significant improvement in positive mood scores (P=0.0001) and a decrease in negative mood scores (P=0.0001) without significant between-group differences. Minimal skin irritation at the application site was seen in 5.7 and 5.3% of patients in the testosterone gel 50 and 100 mg group. Minimal to severe skin irritation occurred in 65.8% of patients in the testosterone patch group. Mean serum PSA levels significantly increased with testosterone gel 100 mg (P=0.008) and testosterone gel 50 mg (P=0.05) with no significant increase with testosterone patch. As a group, both Hgb and Hct increased (P=0.0001) with statistical significance across treatment groups (P=0.0001). There were no overall treatment effects or intergroup differences in serum concentrations of TC, HDL-C, LDL-C or TG (data not provided). Secondary: Not reported
Wang et al.[39] (2004) Testosterone gel (AndroGel®) 50 mg daily vs	ES, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years of age, single morning serum testosterone level	N=163 36 months	Primary: Mean changes from baseline in serum testosterone, free testosterone, DHT, E2, SHBG, LH and FSH; mean changes from baseline in	Primary: Mean serum testosterone levels were significantly different (P=0.012) between dosing groups at baseline (six months of testosterone replacement therapy). At 12 months, differences among the dosing groups became smaller but remained significant (P=0.042). Serum free testosterone levels followed the same pattern as testosterone. Mean serum DHT levels were different in the three dosing groups at 12

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
testosterone gel (AndroGel®) 75 mg daily vs testosterone gel (AndroGel®) 100 mg daily	at screening ≤10.4 nmol/L		sexual function and mood, body composition, bone turnover markers, muscle strength and BMD; mean changes from baseline in Hgb, Hct, lipid profiles and blood chemistries; mean changes from baseline in serum PSA and prostate disease; safety Secondary: Not reported	(P=0.0031) and 24 (P=0.018) months with the highest levels seen with testosterone gel 100 mg. Mean serum E_2 levels progressively increased from six to 24 months (P=0.0001) with significant differences between groups. The highest levels of serum E_2 were seen with testosterone gel 100 mg. No significant change in SHBG was seen. Suppression of LH and FSH was maintained throughout with no significant changes after six months. The suppression was more pronounced with testosterone gel 100 mg. Significant improvements in sexual desire, enjoyment with or without a partner, percent full erection and self-assessment of satisfaction with erections were maintained as a group throughout the study period. Positive mood scores were improved with treatment and were sustained (P=0.0022). Negative mood parameters were decreased and remained significantly lower (P=0.0013) than baseline without further changes after six months. Average total body mass increased by 1.2+0.3 kg at six months (P=0.0157) and did not significantly change with continued therapy. LBM increased significantly (P=0.0001) from baseline and remained increased throughout the study. A significant decrease in fat mass was seen at 30 months (P=0.088) without significant differences between doses. Serum PTH levels significantly increased from baseline (P=0.0001) and continued to increase from six (P=0.0002) until 12 months when it remained stable throughout the rest of the treatment period. Serum SALP levels followed the same pattern (P=0.001). At 12 months serum osteocalcin was significantly elevated and remained elevated throughout treatment (P=0.0001). Serum procollagen levels transiently increased then steadily increased from six months to reach significant levels by 36 months (P=0.0001). Muscle strength increased but did not reach significance over time due to the large variation in patients. BMD of the hip (P=0.0004) and spine (P=0.0001) showed a gradual and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				progressive increase with treatment. No significant differences among treatment doses or older and younger patients were observed. Serum Hgb and Hct concentrations increased, compared to month zero (P=0.0001) and month six (P=0.001) and plateaued at 12 months. Small statistically significant increases in serum HDL-C levels (P<0.001), creatinine (P<0.001) and total bilirubin (P=0.001) were seen but were not clinically significant. No significant changes in TC, LDL-C, serum liver enzymes, or other clinical chemistry parameters were observed. The mean serum PSA was 1.11+0.08 at six months and showed no further significant increases with continued treatment. Application-site reactions occurred in 12 of the 163 (7.4%) patients. Acne occurred in 12 (7.4%) of patients and gynecomastia was observed in eight more patients. Secondary: Not reported
Grober et al.[40] (2008) Testosterone gel (AndroGel®) 5 to 10 g vs testosterone gel (Testim®) 5 to 10 g	OL Hypogonadal men on testosterone gel who underwent a brand substitution due to initial suboptimal biochemical or symptomatic response, mean age of men switched to Testim® was 60, mean age of men switched to AndroGel® was 52	N=370 Treatment duration after switch, 4 weeks	Primary: Reasons for brand substitution, total and free testosterone, presence of hypo-gonadal symptoms Secondary: Not reported	Primary: Of the 370 hypogonadal men using testosterone gel, 20% underwent a brand substitution. The reasons for switching from AndroGel® to Testim® (N=62) were poor efficacy (92%), hypertension (2%), skin reaction (2%), worsening symptoms (2%) and insurance coverage (2%). The reasons for switching from Testim® to AndroGel® (N=13) were scent (46%), poor efficacy (30%), fear of transfer to partner (8%), flushing (8%) and skin reaction (8%). Prior to substitution, patients initially treated with AndroGel®, had mean total and free testosterone levels of 311.0 ng/dL and 10.4 pg/mL, respectively. Total testosterone levels were <300 ng/dL in 58% of these patients. Following a change to Testim®, mean total and free testosterone levels increased to 484.0 ng/dL (P<0.001) and 14.6 pg/mL (P=0.01), respectively. Total testosterone levels remained <300 ng/dL in 17% of these patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Among patients initially treated with Testim®, the mean total and free testosterone levels were 544.0 ng/dL and 18.0 pg/dL, respectively. Total testosterone levels were <300 ng/dL in 15% of men. Following a change to AndroGel®, mean total and free testosterone levels were 522.0 ng/dL (P=0.7) and 16.1 pg/mL (P=0.6), respectively. Total testosterone levels remained <300 ng/dL in 27% of these patients. Secondary: Not reported
Dobs et al.[41] (2012) Testosterone gel (Fortesta®) 40 mg applied to the thighs once daily Dose adjustments allowed for a downward titration to a minimum of 10 mg daily and an upward titration to 70 mg daily.	MC, OL Men 18 to 75 years of age, with primary or secondary hypo-gonadism (defined as a single serum testosterone concentration <250 ng/dL or two consecutive serum testosterone levels <300 ng/dL at least one week apart) and a BMI ≥22 and <35 kg/m^2	N=149 90 days	Primary: The average serum total testosterone concentration over 24 hours (average concentration 0 to 24 hours) on day 90 Secondary: The maximum serum testosterone concentration (C_{max}) on day 90	Primary: Of the 129 patients with available data for analysis, the mean average concentration over 24 hours was 438.56±162.51 ng/dL with 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal physiological range (≥300 and ≤1,140 ng/dL) (95% CI, 70.3 to 84.7). By day 35, 76.2% (95% CI, 68.8 to 83.6) of patients had reached the primary endpoint. On day 90, 22.5% of patients had a total testosterone level <300 ng/dL. Secondary: The maximum concentration±SD was 827.6±356.5 ng/dL on day 90. At endpoint, a total of 94.6% of patients achieved a maximum concentration ≤1,500 ng/dL, 1.6% of patients had levels between 1,880 and 2,500 ng/dL, and no patients had levels >2,500 ng/dL. This maximum concentration was evident by treatment day 35. Adverse events were reported in 46.3% of patients; however on 22.8% were considered related to the study medication. The most commonly reported adverse events were skin reactions, upper respiratory infections and sinusitis. Skin reactions were considered 'possibly' or 'probably' related to study medication in 16.1% of patients, of which 79.2% were mild in severity.
McNicholas et al.[42] (2003) Testosterone gel (Testim®) 50 mg daily in the morning	AC, DB, MC, OL, RCT Hypogonadal men, 31 to 80 years of age, morning	N=208 90 days	Primary: 24-hour pharma-cokinetics profiles at 30, 60 and 90 days; treatment effectiveness as	Primary: At 90 days, mean increases in serum testosterone levels were significant for testosterone gel 100 mg (12.41 nmol/L) over testosterone gel 50 mg (6.54 nmol/L; P<0.05) and testosterone patch (3.82 nmol/L; P<0.001). Results at 30 and 60 days were consistent with those at 90 days. The same results were also seen with the mean increase from baseline in free

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Andropatch®‡) 2.5 mg two patches daily in the morning	serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone		measured by body composition, mood and sexual function data at 30, 60 and 90 days; safety Secondary: Not reported	testosterone levels. At 90 days, the mean change in DHT levels with testosterone gel 100 mg were significant over testosterone gel 50 mg (P<0.05) and testosterone patch (P<0.001). In addition, the mean change in DHT levels with testosterone gel 50 mg was also significant over testosterone patch at 90 days (P<0.001). Results at 30 and 60 days were consistent with those at 90 days. Significant within-treatment group changes in LBM were seen for all three treatment groups; 0.9 (P<0.05), 1.5 kg (P<0.001) and 1.0 kg (P<0.05) for testosterone gel 50 mg, testosterone gel 100 mg and testosterone patch, respectively. Significant within-treatment group mean changes in percentage fat were only seen with testosterone gel 100 mg (–0.7; P<0.05). There were no statistically significant changes in BMD within any of the three treatment groups. No significant differences in improvement in positive mood were seen among the three treatment groups. There were significant differences between treatment groups at 90 days in the alleviation of negative mood favoring testosterone gel over the testosterone patch (P<0.05). At 90 days there were significant within-treatment group improvements from baseline in all three groups in sexual motivation, sexual desire and sexual performance (P<0.05). Both testosterone gel groups had a statistically significant within-treatment improvement in spontaneous erections at all times from baseline (P<0.05). Testosterone patch produced no significant improvement in spontaneous erections at any time. The incidence of treatment-emergent adverse events was 35% for testosterone gel 50 mg, 29% for testosterone gel 100 mg and 63% for testosterone patch groups. The most commonly reported adverse events were erythema, irritation and reactions at the application site. Secondary: Not reported
Steidle et al.[43]	AC, DB, MC, OL,	N=406	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Androderm®) 2.5 mg 2 patches daily in the morning vs placebo	PC, RCT Hypogonadal men, 20 to 80 years of age, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone	90 days	Periodic 24-hour pharmacokinetics profiles; effect of normalizing serum testosterone on body composition, sexual function, mood and BMD; safety Secondary: Not reported	At 30 days, all treatment groups had increased mean serum testosterone and DHT concentrations. Testosterone gel 100 mg had a significant increase in mean changes in testosterone concentrations over the testosterone patch (P<0.001). Testosterone gel 50 and 100 mg resulted in significant increases in mean changes in DHT concentrations compared to the testosterone patch (P<0.001 for each comparison). By 90 days, similar results were seen across treatment groups. At 90 days, mean change in LBM was 1.5±4.5, 1.7±2.6, 0.9±1.8 and 0.6±1.8 kg for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch and placebo, respectively. Increases in LBM were significantly higher for testosterone gel 100 mg than the testosterone patch and placebo (P<0.05 for each comparison). With the exception of placebo treatment, all treatments resulted in a significant decrease in fat mass compared to placebo (P<0.01). At 90 days, when compared to placebo, testosterone gel 100 mg had significant improvements in spontaneous erections (P<0.001), sexual motivation (P<0.05), sexual desire (P<0.01) and sexual performance (P<0.05). No other treatment groups had significant improvements compared to the placebo group. All treatments resulted in mean improvements from baseline in both positive and negative mood scores with no significant differences among the treatment groups. The incidence of treatment-related adverse events was 29.1, 36.9, 62.7 and 40.4% for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch and placebo, respectively. At 90 days, clinically notable decreases in TC, LDL-C and HDL-C were seen with testosterone gel 100 mg (P value not reported). Increases in Hgb and Hct were the highest with testosterone gel compared to the testosterone patch and placebo. Increases in PSA values were highest in the testosterone patch group (6.6%). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Brock et al.[44] (2016) Testosterone 2% topical solution 60 mg once daily vs placebo solution once daily	DB, MC, PC, RCT Males ≥18 years of age with total testosterone <300 ng/dl and at least one symptom of testosterone deficiency (decreased energy and/or decreased sexual drive)	N=715 16 weeks	Primary: Proportion of hypogonadal men with serum total testosterone within the normal range of 300 to 1,050 ng/dl after 12 weeks of treatment Secondary: In participants with low sex drive to assess the impact of testosterone on levels of sexual arousal, interest and drive as measured using Sexual Arousal, Interest and Drive scale; and in participants with low energy to assess the impact of testosterone on levels of energy as measured using Hypogonadism Energy Diary	Primary: Overall, 297 of 302 participants assigned to testosterone and 287 of 294 assigned to placebo underwent testosterone measurement at week 12. Of testosterone and placebo completers 73% and 15%, respectively, were within the normal range at week 12 (P<0.001). Secondary: In the subset with low sex drive at baseline participants assigned to testosterone showed a statistically significant baseline to end point improvement in Sexual Arousal, Interest and Drive scores vs those assigned to placebo (P<0.001). In the subset with low energy at baseline participants assigned to testosterone showed a significant baseline to end point improvement in Hypogonadism Energy Diary scores vs those assigned to placebo (P=0.02), but the difference did not reach the prespecified significance level of P<0.01.
Wang et al.[45] (2011) Testosterone topical solution (Axiron®) 60 mg applied to each axilla once	OL with ES Men ≥18 years of age with androgen deficiency (diagnosis of hypogonadism)	N=155 OL study 120 days N=71 ES	Primary: Total testosterone and DHT (OL phase) Secondary: PDQ domain	Primary: At day 120, the proportion of patients completing the study with an average testosterone concentration (average concentration) in the normal range was 84.1%. Also, 76.1 and 84.8% of patients completed the study with an average concentration in the responder range on days 15/16 and 60/61, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily	and a BMI <35.0 kg/m^2 with testosterone levels on two consecutive samples <10.4 nmol/L and a baseline Hgb level ≥1,10.5 g/L	60 days	assessing sexual desire, enjoyment and performance, sexual activity and mood, SF-36 health survey (ES phase)	The mean serum testosterone level before and after dosing was within the adult male range over the 24-hour period on days 15, 60 and 120. The geometric mean of serum testosterone over 24 hours was 15.62 nmol/L (coefficient of variation; 38%). Among subjects who were responders at day 120, the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. Serum DHT levels and serum free testosterone remained relatively stable over the 24-hours following dosing. The mean day 15 baseline pre-dose DHT/testosterone ratio was 0.23, and the mean DHT/testosterone ratio remained between 0.17 and 0.26 throughout the 24-hour period. The ratio values among patients completing the study and among responders remained relatively constant from baseline. Secondary: Improvements in sexual desire and activity were apparent 15 days after application of testosterone and were sustained throughout the study. Statistically significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood as assessed by the PDQ domain for the seven days prior to visits one, 15, 60 and 120. Significant mean changes from day one to 120 for SF-36 Physical Component and SF-36 Mental Component scores were 1.55 (SD, 7.72; P=0.0254) and 4.54 (SD, 9.20; P<0.0001), respectively. Treatment-emergent adverse events occurring in >2% of patients receiving at least one dose of testosterone in the OL study included: application site irritation, application site erythema, headache, increased Hct, nasopharyngitis, diarrhea and vomiting. Three patients withdrew from the OL phase of the study due to adverse events, including superficial thrombophlebitis, effects on lability/anger and malignant melanoma; while two patients withdrew from the extension phase of the study due to application site irritation and application site erythema.
Rogol et al.[46] (2015) Testosterone nasal gel 4.5% (Natesto®)	MC, OL, RCT Men 18 to 80 years of age with two fasting morning	N=306 90 days	Primary: Percentage of patients with serum total testosterone average	Primary: The percentages of intent-to-treat subjects whose total testosterone C_{avg} were in the normal range was 73% (95% CI, 68 to 79) in the total population, 68% (95% CI, 61 to 74) in the titration arm, and 90% (95% CI, 83 to 97) in the fixed-dose arm.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fixed-dose arm (TID, 5.5 mg/nostril, 11 mg/dose, 33 mg/day) vs Testosterone nasal gel 4.5% (Natesto®) titration arm, starting at twice daily (BID, 22 mg/day) with potential dose adjustment to TID (33 mg/day)	total serum testosterone levels <300 ng/dL, BMI between 18.5 and 35 kg/m^2, and hemoglobin level ≥13.0 g/dL		concentration value within the eugonadal range (≥300 ng/dL, ≤1050 ng/dL) Secondary: Number and percentage of subjects with a serum total testosterone C_{max} in pre-specified categories: ≤1500 ng/dL, ≥1800 and ≤2500 ng/dL, and >2500 ng/dL	The mean total testosterone C_{avg} increased from 200.8 ng/dL at baseline into the normal range in all groups after 90 days of treatment. Mean total testosterone C_{avg} were 375 and 421 ng/dL for BID and TID regimens, respectively. Among subjects whose C_{avg} value was in the normal range, the mean values were 415 ng/dL for the BID and 428 ng/dL for the TID regimens. Secondary: In the intent-to-treat population, 88.6% of patients had mean testosterone C_{max} at Day 90 below 1500 ng/dL. Nine (3.3%) subjects had C_{max} between 1800 and 2500 ng/dL. One subject showed a C_{max} >2500 ng/dL (3570 ng/dL); this subject, presumably did not discontinue concomitant finasteride treatment prior to the study as evidenced by lab values.
Sih et al.[47] (1997) Testosterone cypionate 200 mg intramuscularly biweekly vs placebo	DB, PC, RCT Hypogonadal men with testosterone <60 ng/dL, mean ages 65 to 68 in the treatment arms	N=32 12 months	Primary: Changes in grip strength, Hgb, Hct, PSA, leptin and memory Secondary: Not reported	Primary: Testosterone cypionate improved bilateral grip strength (P<0.05) and increased Hgb compared to placebo (P<0.001). The men assigned to testosterone cypionate had greater decreases in leptin than those assigned to placebo (P<0.02). There were no significant changes in PSA or memory (P values not reported). Three men receiving placebo withdrew from the study. Seven men receiving testosterone cypionate withdrew from the study of which three were due to abnormal elevations in Hct. Secondary: Not reported
Snyder et al.[48] (1980) Testosterone	OL Men 24 to 67 years of age with	N=23 12 to 16 weeks	Primary: Changes in serum testosterone, FSH and LH levels	Primary: All four regimens produced serum testosterone concentrations that fluctuated largely within the normal range; the average concentration between doses was highest with 100 mg and lowest with 400 mg (P values

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enanthate 100 mg intramuscularly once a week (n=12) vs testosterone enanthate 200 mg every two weeks (n=10) vs testosterone enanthate 300 mg every three weeks (n=9) vs testosterone enanthate 400 mg every four weeks (n=6)	primary hypogonadism defined by testosterone <300 ng/dL, FSH >14 mIU/mL and LH >18 mIU/mL		Secondary: Not reported	not reported). The regimens of testosterone enanthate 200 mg every two weeks and 300 mg every three weeks appeared to be the most effective of those tested in terms of suppression of serum LH concentration to normal and in frequency of administration. Testosterone enanthate 100, 200 and 300 mg regimens all suppressed the initially elevated serum LH concentrations to normal, but not the 400 mg regimen. Testosterone enanthate 100 and 200 mg regimens suppressed the initially elevated serum FSH concentrations to normal, but not the 300 and 400 mg regimens (P values not reported). Secondary: Not reported
Kaminetsky et al.[49] (2019) Testosterone enanthate auto-injector 75 mg subcutaneous self-administered weekly Dose adjustments were made at week 7 to 50, 75 or 100	OL Men diagnosed with hypogonadism	N=150 52 weeks	Primary: Percent of patients with total testosterone average concentration during 7-day dosing interval within the defined range of 300 to 1,100 ng/dl (endpoint met if 75% of patients achieve at week 12)	Primary: The primary end point was met since 92.7% of patients achieved an average total testosterone concentration of 300 to 1,100 ng/dl (mean ± SD 553.3 ± 127.29) at week 12. Secondary: A maximum concentration of less than 1,500 ng/dl was achieved by 91.3% of patients and no patient had a level greater than 1,800 ng/dl at week 12. The mean total testosterone trough concentration was 487.2 ± 153.33 ng/dl at week 52. The most frequently reported treatment emergent adverse events were increased hematocrit, hypertension and increased prostate specific

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg testosterone enanthate			Secondary: Additional total testosterone concentrations, adverse events	antigen, which led to discontinuation in 30 men. There were no study drug related serious adverse events. Injection site observations experienced by greater than 8% of patients included erythema, pinprick/needle mark and pressure mark from the needle guard.
Zitzmann et al.[50] (2013) IPASS Testosterone undecanoate treatment (initial intramuscular injections with a 6-week interval, the following intervals between two injections are almost always 12 weeks)	OS, PRO, Post-Authorisation Surveillance Study Men diagnosed with hypogonadism (aged 49.2 ± 13.9 years)	N=1,438 Patients received up to five testosterone undecanoate injections during 9 to 12 months.	Primary: Parameters of erectile function, libido, vigor/ vitality, mood, and ability to concentrate assessed by physician interview. Physical and circulatory parameters as well as hematocrit, PSA levels, glucose control, and lipid profiles Secondary: Not reported	Primary: There was a significant improvement of the overall levels of sexual desire/libido: a very low/low level at baseline decreased from 64% of patients to 13% after two injections and to 10% at the time of injection 5. A high/very high level of libido increased from 10% of patients at baseline to 42% after two injections to 61% at the time of injection 5 (overall chi-square test: P<0.0001). Improvements in vigor/vitality, mood, and ability to concentrate showed significant improvements. Blood pressure and serum lipid profiles changed during treatment in a favorable and significant manner. PSA exceeded 4 ng/mL in 11 men. There were clinical reasons to perform a prostate biopsy in four cases, but in no case prostate cancer was observed. Hematocrit rose gradually from 42.8 ± 6.6% at baseline to 44.5 ± 6.1% at the time of injection 5 (P<0.0001). Secondary: Not reported
Tan et al.[51] (2013) Testosterone undecanoate intramuscular injection every 10 to 14 weeks vs placebo	DB, PC, RCT Men in Malaysia aged 40 to 70 years, with testosterone deficiency (serum total testosterone ≤12 nmol/L) and a PSA <4 ng/mL within the past year	N=114 48 weeks	Primary: Hemoglobin, hematocrit, serum total testosterone, lipid profile, fasting blood glucose, sex hormone-binding globulin, liver function test, PSA, and adverse events Secondary: Not reported	Primary: Significant increase in serum total testosterone (P<0.001), PSA (P=0.010), hematocrit (P<0.001), hemoglobin (P<0.001) and total bilirubin (P=0.001) were seen in the treatment arm over the 48-week period compared with the placebo group. A total of 26 (44.8%) men in the control group and 19 (33.9%) men in the treatment group reported adverse events. The most common adverse event in both groups were itching, swelling or pain at the site of injection (control group: n=16 [39.0%] vs treatment group: n=7 [25.9]). Secondary: Not reported
Hackett et al.[52]	DB, PC, RCT	N=190	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) Testosterone undecanoate (TU) 1,000 mg intramuscularly at week 0, 6, and 18 vs placebo	followed by OL Men aged 18 and over from the type 2 diabetes registers of the eight general practices based on the initial finding of either total testosterone (TT) between 8.1 and 12 nmol/L or free testosterone (FT) from 0.181 to 0.25 nmol/L (mild group) or TT of 8.0 nmol/L or less or FT of 0.18 nmol/L or less (severe group).	DB, PC for 30 weeks, followed by 52-week OL	International Index of Erectile Function (IIEF) Secondary: Aging Male Symptom (AMS), Hospital Anxiety and Depression Scale (HADS), and Global Efficacy Question	Testosterone replacement therapy with long-acting TU improved all domains of sexual function at 30 weeks (erectile function [EF], P=0.005; intercourse satisfaction, P=0.015; sexual desire, P=0.001; overall satisfaction, P=0.05; and orgasm, P=0.04), with benefit as early as 6 weeks. Secondary: Improvements in AMS score were significant in men without depression (P=0.02) and the presence of depression at baseline was associated with marked reduction in response to both sexual function and psychological scores. All responses in sexual function continued to improve significantly up to 18 months with an improvement in EF score of 4.31 from baseline. In a small cohort of 35 men taking phosphodiesterase type 5 inhibitors, there was no change during the double-blind phase but a nine-point improvement in EF domain during 52-week open-label treatment. After 30 weeks, 46 vs 17% of patients on active therapy vs placebo felt that the treatment had improved their health, reaching 70% after open-label therapy. Less obese and older patients responded better to testosterone therapy. There were no significant adverse events.
Swerdloff et al.[53] (2020) Testosterone undecanoate 158 to 396 mg orally twice daily vs testosterone (Axiron®) 30 to 129 mg topically once daily	AC, OL, RCT Men 18 to 65 years of age with BMI <38 kg/m^2, with hypogonadism as defined by consistently low morning serum total T <300 ng/dL and a history of signs and/or symptoms consistent with hypogonadism	N=221 4 months	Primary: Percentage of patients with mean testosterone concentration over 24 hours within the normal eugonadal range on the final visit of the study Secondary: Peak testosterone concentration	Primary: 87.3% of patients in the oral testosterone undecanoate group had mean testosterone concentration values in the eugonadal range, with a mean ±SD value of 403 ±128 ng/dL (14 ±4 nmol/L) based on testosterone assay of sodium fluoride-ethylenediamine tetra-acetate plasma. Of those patients dosed with topical testosterone, primary efficacy identical to oral testosterone undecanoate was observed (i.e., 87.3%) based on final visit testosterone assays, with a mean ±SD value of 391 ±140 ng/dL. Secondary: At the end of the study, values of testosterone peak testosterone concentration ≤1,500 ng/dL were observed for 90.7% of patients in the oral testosterone undecanoate group and 97.9% of patients in the topical testosterone group. None of the patients treated with oral testosterone undecanoate experienced a peak testosterone concentration value >2,500 ng/dL except for three spurious and transient peak testosterone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				concentration excursions above 2,500 ng/dL that were determined to be the result of external contamination of the 2-hour post-dose plasma samples at a single study site where plasma samples were being prepared from topical testosterone patients at the same time as samples from those dosed with oral testosterone undecanoate.
Endometriosis				
Selak et al.[54] (2007) Danazol 200 mg three times a day alone or as adjunctive therapy vs placebo	MA of 5 RCT (literature search included Medline 1966 to April 2007) Women of reproductive age with the diagnosis of endometriosis made by direct visualization (mean ages 28 to 33)	N=370 Treatment: 3 to 6 months; Follow-up: 6 to 36 months	Primary: Improvement in pain Secondary: Changes in AFS scores and safety	Primary: One study found a significant decrease in the levels of pelvic pain, lower back pain, defecation pain and total pain in patients treated with danazol without surgery compared to those treated with placebo, at three and six months of therapy and six months after medication (P values not reported). In patients receiving danazol and surgery, a significant decrease in the levels of total pain and pelvic pain was reported compared to placebo at six months of therapy (P values not reported). This improvement in pain scores was still present six months after the end of therapy with danazol. Secondary: Two studies examined the change in AFS scores at repeat laparoscopy six months after the end of medication. While there was no significant difference in total AFS score, danazol without surgery caused a decrease in peritoneal AFS scores (P values not reported). In patients treated with danazol and surgery, a significant decrease in total and peritoneal AFS scores compared to placebo was noted (P values not reported). Only one study evaluated adverse effects. This study found a significant increase in acne, muscle cramps and edema in women receiving danazol without surgery at six months (P value not reported). When danazol was used with surgery, a significant increase in acne, weight gain and spotting was reported at 6 months (P value not reported).
Beaumont et al.[55] (2007) Danazol vs	MA (9 RCTs) Women of reproductive years with regular heavy menstrual blood loss and recruited	N=353 ≤3 months	Primary: Reduction in objectively measured menstrual blood loss during and after intervention,	Primary: One trial compared danazol to placebo; however, menstrual blood loss, duration of menses could not be assessed for differences. There were no significant differences between the danazol and placebo groups in withdrawals due to side effects (P=0.56). Five trials compared danazol with a progestin (norethisterone or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
other medical therapy (norethisterone, mefenamic acid, progesterone intrauterine device, medroxy-progesterone, low-dose oral contraceptives) vs placebo	from primary care, family planning or specialist clinic setting		reduction in subjectively measured blood loss by the woman, QOL, side effects, withdrawals, reduction in symptoms of dysmenorrhea Secondary: Weight gain, subjective efficacy of intervention, subjective time to relapse, duration of menses, resources use (women, general practitioner, hospital, health service	medroxyprogesterone). For one trial measuring mean menstrual blood loss, there was no significant difference between the groups. For two trials measuring weight gain as a QOL outcome, there were no significant differences between the groups. In one trial that evaluated the interventions at a three month follow up, the progestin group has significantly lower menstrual blood loss (P=0.025). Two trails compared different doses of danazol; however, there were no significant differences in outcomes. Three trials compared danazol with mefenamic acid. There was no significant difference in the improvement of dysmenorrhea between the groups. There were significantly more side effects reported in the danazol group compared to mefenamic acid group (P=0.0062). However, in a trial evaluating acceptability of treatment, there was no significant difference between the groups. Mean menstrual blood loss was significantly lower in the danazol treatment groups compared to mefenamic acid (P<0.00001). One trial compared danazol with an oral contraceptive. Menstrual blood loss was significantly lower in the danazol group after two months (P=0.02). Secondary: In the trial comparing danazol to placebo, weight gain was significantly greater than in the danazol group compared to placebo (P=0.022). For the trials comparing danazol to a progestin, there were significantly more patients in the danazol group rating as high or moderate efficacy (P=0.037); whereas, another trial found no significant difference with rating menstrual blood loss as none or moderate (P=0.10). There were significantly more patients in the danazol group compared to the progestin group that reported side effects (P=0.0030). There was no significant difference in duration of menses and withdrawals due to side effects between the groups. Mean weight gain was significantly higher with danazol compared to progestins (P<0.00001) in the one trial measuring this outcome. In one trial objectively measuring menstrual blood loss, danazol had lower menstrual blood loss compared to progestins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.025). In the trials comparing danazol to mefenamic acid, the duration of menses was significantly shorter in the danazol group compared to mefenamic acid group (P=0.0074). One trial compared danazol to a progesterone intrauterine device. The duration of menses was significantly shorter in the danazol group (P<0.0001).
Hereditary Angioedema				
Gelfand et al.[56] (1976) Danazol (dose not reported) vs placebo	DB Patients with hereditary angioedema (age not reported)	N=9 Duration not reported	Primary: Number of attacks of hereditary angio-edema, safety and changes in biochemical markers Secondary: Not reported	Primary: Prophylaxis with danazol resulted in only one attack per 46 danazol courses compared to 44 attacks per 47 placebo courses (P value not reported). Side effects were minimal, and virilization was not observed in the women studied. Danazol increased C1 esterase inhibitor levels by three to four folds and levels of the fourth component of complement by 15 folds. These changes began during the first day of therapy and were maximal by the first one to two weeks. After therapy was stopped, C1 esterase inhibitor and fourth component of complement levels rapidly decreased. Secondary: Not reported
Bork et al.[57] (2008) Danazol (dosage range from 100 mg to >600 mg per day)	RETRO Male and female patients with a mean age of 33 with hereditary angioedema	N=118 2 months to 30 years	Primary: Frequency and severity of acute attacks before and during danazol therapy and safety Secondary: Not reported	Primary: In all, 94.1% of patients responded to danazol. During treatment, 45.8% of patients became symptom free or had one attack or less per year. In the other patients, hereditary angioedema ran a mild course. The frequency of acute attacks during danazol treatment was reduced to 16.2%, and the attacks were considerably milder than before treatment. Laryngeal edema was reduced to 4.8%. Adverse effects (depression, headache, menstrual irregularities, liver adenomas and virilization) occurred in 78.8% of patients and led to discontinuation of danazol therapy in 25.4% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Weight Gain				
Porro et al.[58] (2012) Oxandrolone 0.1 mg/kg twice daily for 12 months vs placebo	RCT Children 0 to 18 years of age at the time of burn with >30% total body surface area affected and the need for at least one surgical intervention	N=222 5 years	Primary: Changes from baseline in growth, body composition, muscle strength, resting energy expenditure, liver and cardiac function, serum markers, hormones, bone mass and sexual maturation Secondary: Changes in bone-age and psychosocial function	Primary: There was a significant decrease in percent predicted resting energy expenditure in patients treated with oxandrolone (P<0.01). There was a significant difference between the oxandrolone and placebo groups until six months post-burn (P<0.004). The percentage of patients >2 SDs below mean high velocity was significantly different between the oxandrolone and placebo groups at year one (8 vs 48%; P<0.05) and year two (7 vs 32%; P<0.05), but not at years three, four, and five. Patients in the placebo group had negative percent change in height velocity compared to a positive percent change with patients treated with oxandrolone (P<0.05). The percentage of patients >2 SDs below mean weight velocity was significantly lower in the oxandrolone group compared to the placebo group at year one (28 vs 46%; P<0.05) but not at any other year. There was a significant higher change in bone mineral content in the oxandrolone group compared to the placebo group in patients seven to 18 years of age from years two through five (P<0.001). There were no significant differences in patients <7 years of age. BMD was not significantly different between the groups. LBM was not significantly different between the groups (P=0.06). Serum constitutive proteins, prealbumin, retinol-binding protein, and transferrin were significantly higher in the oxandrolone treated patients compared to placebo (P<0.05). Serum albumin and total protein were not significantly different between the groups. IGF-1 was significantly higher in the oxandrolone group compared to placebo from discharge to two years (P<0.05). There were no differences in IGFBP-3 between the groups. There were no significant differences in PTH, free thyroid index, and T3 uptake. The cardiac output, percent predicted cardiac output, percent predicted

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				heart rate were significantly lower in the oxandrolone group compared to placebo at year one (P<0.05). Percent predicted cardiac output and heart rate were also significantly lower at year two in in the oxandrolone group compared to placebo (P<0.05). Liver length and weight were not significantly different between the groups. Secondary: There was no significant difference in bone age between the groups. There was no effect of oxandrolone on psychosocial outcomes.
Grunfeld et al.[59] (2006) Oxandrolone 20 mg once daily vs oxandrolone 40 mg once daily vs oxandrolone 80 mg once daily vs placebo During the OL extension phase, all patients were switched to 20 mg once daily.	DB, MC, PC, PG, RCT (OL extension) HIV-infected men ≥18 years of age with 10 to 20% unintentional weight loss from premorbid weight documented in medical records or BMI ≤20 kg/m^2, a Karnofsky Performance Scale score >60%, a life expectancy of >6 months, and the ability to consume a normal well-balanced diet	N=262 12 weeks (DB) 12 weeks (OL)	Primary: Change from baseline in body weight at two, four, eight and 12 weeks in DB phase and at 14, 18 and 24 weeks in OL phase Secondary: Change from baseline of fat and BCM at all time points, health-related QOL, physical capability at weeks two and 12, and safety measures of HIV RNA levels, CD4 counts, complete blood counts and blood chemistry	Primary: There were significant increases in body weight for all groups (including placebo) as soon as two weeks and continuing through 12 weeks (P<0.014 vs baseline at 12 weeks). When compared to placebo, weight gain was significantly greater in patients treated with oxandrolone 40 mg at weeks two, four, eight and 12 (P<0.0040 for all comparisons). Weight gain in the patients treated with 80 mg was significantly greater than placebo at weeks four and eight (P<0.017 for both), but not significantly different at weeks two and 12 (P=0.045 for 12 weeks). During the OL extension phase, all patients continued to gain weight; however, the weight gain was not significantly different between the groups. Secondary: There were significant increases in BCM compared to baseline in all groups (P value not reported). There were significantly greater increases in BCM compared to placebo in patients treated with 40 mg (P<0.0049) and 80 mg (P<0.0002) at 12 weeks. There were no significant differences in fat in any group. There were no significant differences in health-related QOL and physical capacity for any treatment group. There was a dose-dependent increase in platelet count in patients treated with oxandrolone compared to placebo (P<0.017 for all doses of oxandrolone vs placebo). There were significant increases in creatinine and creatine kinase in patients treated with oxandrolone compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (P<0.017 for all doses of oxandrolone vs placebo). Compared to placebo, there were dose dependant significant increases in ALT for patients treated with 40 and 80 mg (P<0.017 for both doses) and AST for patients treated with 80 mg (P<0.017). There were significant decreases in uric acid and HDL in patients treated with all doses of oxandrolone (P<0.017 for all comparisons). For patients treated with 40 and 80 mg, there were significant increase in LDL compared to placebo (P<0.017 for both). There were no significant differences in other measures.
Mwamburi et al.[60] (2004) Oxandrolone 10 mg twice daily vs megestrol 800 mg once daily	RCT HIV positive men and women (average age 40 years) receiving stable highly active antiretroviral therapy that unintentionally lost ≥5% of their body weight during the preceding six months	N=40 2 months	Primary: Change from baseline in body weight and composition Secondary: Patient tolerance and adverse event profile	Primary: Compared to baseline, there were statistically significant increases in total body weight, BMI, and LBM for the oxandrolone group (P=0.001; P=0.001; P=0.04) and the megestrol group (P=0.01; P=0.005; P=0.02). There were no significant differences between the treatment groups in any measure. Secondary: The most common adverse effects in patients treated with megestrol were nausea and vomiting and feeling bloated and swollen. The most common adverse event reported with oxandrolone was elevated transaminases.

‡Agent not available in the United States.
Study abbreviations: AC=active-controlled, BID=twice daily, CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SD=standard deviation, TID=three times a day
Miscellaneous abbreviations: AFS=American Fertility Society, ALT= alanine aminotransferase, AST= aspartate aminotransferase, AUC=area under the curve, BCM=body cell mass, BMD=bone mineral density, BMI=body mass index, DHT=dihydrotestosterone, E2=Estradiol, FSH=follicle-stimulating hormone, Hct=hematocrit, HDL=high density lipoprotein, Hgb=hemoglobin, HIV=human immunodeficiency virus, IGF=insulin growth factor, IGFBP=insulin growth factor binding proteins, LBM=lean body mass, LDL=low density lipoprotein, LH=luteinizing hormone, PSA=prostate specific antigen, PTH=parathyroid hormone, QOL=quality of life, RNA=ribonucleic acid, SALP=bone-specific alkaline phosphatase, SF-36=short form-36, SHBG=sex hormone-binding globulin, TC=total cholesterol, TG=triglycerides, vBMD=volumetric bone mineral density

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 14. Relative Cost of the Androgens

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Danazol	capsule*	N/A	N/A	$$$$$
Methyltestosterone	Capsule*, tablet*	N/A	$$$$$	$$$$$
Oxandrolone	tablet*	N/A	N/A	$$$
Testosterone	implant, nasal gel, transdermal gel, transdermal patch, transdermal solution	Androderm®, AndroGel®*, Fortesta®*, Natesto®, Testim®*, Testopel®, Vogelxo®*	$$$$$	$$$
Testosterone cypionate	solution for injection	Depo®-Testosterone*	$$$$$	$$
Testosterone enanthate	solution for injection*	Xyosted®	$$$$$	$$
testosterone undecanoate	capsule, oil for injection	Aveed®, Jatenzo®	$$$$$	N/A

*Generic is available in at least one dosage form and/or strength.
N/A=not available.

X. Conclusions

The androgens are approved for a variety of conditions and, with the exception of danazol and oxandrolone, all agents in this review are Food and Drug Administration (FDA)-approved for the management of male hypogonadism. The oral synthetic testosterone, methyltestosterone, and the injectable testosterone enanthate are also FDA-approved for the treatment of delayed puberty in males and metastatic mammary cancer in females. Danazol is FDA-approved for the treatment of endometriosis, fibrocystic breast cancer and hereditary angioedema, though it is not indicated for the management of male hypogonadism. Oxandrolone is approved for adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain or to maintain normal weight. This agent is also approved to offset the protein catabolism associated with prolonged administration of corticosteroids and for the relief of the bone pain frequently accompanying osteoporosis. [1-16]

In clinical studies, testosterone buccal and topical products have been shown to increase serum testosterone levels and/or improve lean body mass, decrease body fat, and improve sexual function in men with hypogonadism.[22,27-41] Head-to-head studies comparing testosterone topical gel to testosterone transdermal system have shown greater improvement in serum testosterone levels, lean body mass, and sexual function as well as fewer adverse events with testosterone gel compared to testosterone patches in men with hypogonadism.[35-36,40-41] Severe hepatotoxicities have been associated more commonly with oral androgen than topical androgen therapy and liver function tests should be monitored periodically.[1-18] According to current consensus guidelines, intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects. The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, and treatment burden. Furthermore, currently available guidelines do not give preference to one topical preparation vs another.[19,22]

The Testosterone Trials (T Trials) were conducted at 12 sites across the country in 790 men ≥65 years of age with low levels of testosterone and symptoms to which low testosterone might contribute. Participants were randomly assigned to receive testosterone gel or a placebo gel applied to the skin daily. In older men with low testosterone, one year of testosterone treatment improved bone density and corrected anemia of both known and unknown causes, but also increased the volume of coronary artery plaque, according to results reported from the T Trials. Testosterone treatment had no effect on memory or other cognitive function.[28-32]

Currently, danazol, methyltestosterone, oxandrolone, testosterone, testosterone cypionate, and testosterone enanthate are available generically.

There is insufficient evidence to support that one brand androgen is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand androgens within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand androgen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Complement Inhibitors for the Treatment of Hereditary Angioedema (HAE)
AHFS Class 923208
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I. Overview

Hereditary angioedema (HAE) is a disease characterized by recurrent episodes of angioedema which most often affect the skin or mucosal tissues of the upper respiratory and gastrointestinal tracts. The estimated prevalence of the disease is approximately 1 in 50,000 persons worldwide. Patients with HAE experience episodes of swelling due to excess production of bradykinin, a potent vasodilatory mediator. These episodes of swelling typically resolve in two to five days without treatment; however, laryngeal involvement may cause fatal asphyxiation. In HAE, histamine and other mast cell mediators are not directly involved. As a result, patients with HAE have a poor response to antihistamines, which distinguishes this form of angioedema from the histamine-mediated angioedema that is seen in allergic reactions and urticaria.[1,2]

There are several types of HAE. Type I occurs due to a deficiency of C1 esterase inhibitor while Type II occurs due to dysfunction of C1 esterase inhibitor. Other types of familial angioedema are characterized by normal C1 esterase inhibitor and normal complement studies.[1]

Optimal management of HAE includes treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimize the frequency and severity of recurrent attacks.[1-11] The human C1 esterase inhibitors Cinryze® and Haegarda® are approved by the Food and Drug Administration (FDA) for routine prophylaxis against angioedema attacks in adolescents and adult patients with HAE.[3,4] Cinryze® is also approved for use in pediatric patients six years of age and older.[3] Takhzyro® (lanadelumab-flyo) was approved in August 2018 for prophylaxis to prevent attacks of HAE in patients 12 years and older. It is a fully human monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity. Lanadelumab-flyo decreases plasma kallikrein activity to control excess bradykinin generation in patients with HAE.[8] Orladeyo® (berotralstat hydrochloride) was approved in December 2020 for prophylaxis to prevent attacks of HAE in patients 12 years of age and older. It is a dihydrochloride salt that binds plasma kallikrein and inhibits its proteolytic activity.[9]

The human C1 esterase inhibitor Berinert® and the recombinant C1 esterase inhibitor Ruconest® are FDA-approved for the treatment of acute attacks of HAE. Berinert® is approved in pediatric and adult patients for abdominal, facial, or laryngeal attacks, while Ruconest® is approved in adolescent and adult patients for attacks that do not involve the laryngeal area. Icatibant is bradykinin B2 receptor antagonist that is FDA-approved for the treatment of acute attacks of HAE in adults 18 years of age and older. Ecallantide is a human plasma kallikrein inhibitor that reduces the conversion of high molecular weight kininogen to bradykinin and is FDA-approved for the treatment of acute attacks of HAE in patients 12 years of age and older. Ecallantide should only be administered by a healthcare professional.[5-8]

The complement inhibitors for the treatment of HAE that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Icatibant is currently available in a generic formulation. This class was last reviewed in May 2020.

Table 1. Complement Inhibitors for the Treatment of HAE Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Berotralstat hydrochloride	oral capsule	Orladeyo®	none
C1 esterase inhibitor, human	intervenous injection, subcutaneous injection	Berinert®, Cinryze®, Haegarda®	none
C1 esterase inhibitor, recombinant	intervenous injection	Ruconest®	none
Ecallantide	subcutaneous injection	Kalbitor®^	none
Icatibant	subcutaneous injection	Firazyr®*, Sajazir®*	icatibant
Lanadelumab-flyo	subcutaneous injection	Takhzyro®	none

*Generic is available in at least one dosage form or strength.

^ Product is primarily administered in an institution and will not be included in the remainder of this review.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the complement inhibitors for the treatment of hereditary angioedema are summarized in Table 2.

Table 2. Treatment Guidelines for Hereditary Angioedema

Clinical Guideline	Recommendation(s)
International Working Group: **Evidence-based Recommendations for the Therapeutic Management of Angioedema Owing to Hereditary C1 Inhibitor Deficiency (2012)**[12]	Long-term Prophylaxis of Attacks • Based on clinical experience, it has been suggested to consider long-term prophylaxis when patients, despite optimized on-demand treatment of angioedema attacks, continue experiencing more than 12 moderate-to-severe attacks per year or more than 24 days per year affected by HAE. • Three classes of drugs, attenuated androgens, antifibrinolytic agents and plasma-derived C1-INH concentrates, under-went controlled clinical trials against placebo, and these trials proved their efficacy for long-term prophylaxis in HAE. Acute Treatment for Attacks • Acute treatment aims to resolve angioedema symptoms as quickly as possible. • Evidence suggests that the C1-INH concentrates, plasma-derived (Cinryze®), and recombinant (Ruconest®); kallikrein inhibitor, ecallantide (Kalbitor®); and bradykinin B2 receptor antagonist, icatibant (Firazyr®) are suitable for acute attacks. • There are no head-to-head studies available. Goals of Treatment • Reducing morbidity and mortality in HAE must begin with early and accurate diagnosis. • HAE patients should have a specialist familiar with the disease involved in their care. • Treatment for HAE must be individualized to each patient's needs and requests to provide optimal care and restore a normal quality of life to the patient.
Canadian Hereditary Angioedema Network: **The International/ Canadian Hereditary Angioedema Guideline (2019)**[13]	Acute Treatment of HAE-I and HAE-II • Effective therapy should be used for the acute treatment of attacks of angioedema to reduce duration and severity of attacks. • Intravenous pdC1-INH is an effective therapy for the acute treatment of attacks. • Icatibant is an effective therapy for the acute treatment of attacks. • Ecallantide is an effective therapy for the acute treatment of attacks. • Intravenous recombinant human C1-INH is an effective therapy for the acute treatment of attacks. • Attenuated androgens should not be used for the acute treatment of attacks. • Frozen plasma could be used for acute treatment of attacks if other recommended therapies are not available. • Attacks should be treated early to reduce morbidity and mortality. • All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately. Acute Treatment and Short-Term Prophylaxis of HAE in Pregnant Patients • pdC1-INH is the treatment of choice for angioedema attacks in pregnant HAE-I/II patients. Acute Treatment of HAE in Pediatric Patients • All pediatric patients diagnosed with HAE should have access to acute treatment,

Clinical Guideline	Recommendation(s)
	including those that are symptom free. • Intravenous pdC1-INH is an effective therapy for the acute treatment of HAE-I/II attacks in pediatric patients. • Icatibant is an effective therapy for the acute treatment of HAE-I/II attacks in pediatric patients. • Intravenous recombinant human C1-INH is an effective therapy for the acute treatment of HAE-I/II attacks in pediatric patients. • Ecallantide is an effective therapy for the acute treatment of HAE-I/II attacks in adolescent patients. Acute Treatment of HAE with Normal C1-INH • pdC1-INH is an effective therapy for the acute treatment of attacks in patients with HAE with normal C1-INH function. • Icatibant is an effective therapy for the acute treatment of attacks in patients with HAE with normal C1-INH function. Short-term Prophylaxis • Short-term prophylaxis should be considered prior to known patient-specific triggers and for any medical, surgical, or dental procedures. • HAE-specific acute treatment should be available during and after any procedure. • Intravenous pdC1-INH should be used for short-term prophylaxis in patients with HAE. Long-term Prophylaxis in HAE-I and HAE-II • Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration, and severity of attacks. • pdC1-INH is an effective therapy for long-term prophylaxis in patients with HAE-I/II. • Lanadelumab-flyo is an effective therapy for long-term prophylaxis in patients with HAE-I/II. • Subcutaneous C1-INH or lanadelumab-flyo should be used as first-line therapy for long-term prophylaxis in patients with HAE-I/II. • Attenuated androgens and anti-fibrinolytics should not be used as first-line therapy for long-term prophylaxis in patients with HAE-I/II. • Attenuated androgens are an effective therapy for long-term prophylaxis in some patients with HAE-I/II. • All patients should have a management plan including immediate access to effective treatment for attacks, even when on prophylaxis. Long-term Prophylaxis in Pregnant HAE Patients • When long-term prophylaxis is indicated in pregnancy, pdC1-INH is the treatment of choice. • Attenuated androgens should not be used during pregnancy or during the breastfeeding period. Long-term Prophylaxis in Pediatric HAE Patients • When long-term prophylaxis is indicated in pediatric patients, pdC1-INH is the treatment of choice. • Androgens should not be used for long-term prophylaxis in pediatric patients.
World Allergy Organization/ European Academy of Allergy and Clinical Immunology:	On-demand Treatment • All attacks should be considered for on-demand treatment. • Any attack affecting or potentially affecting the upper airway should be treated. • It is recommended that all attacks be treated as early as possible.

Clinical Guideline	Recommendation(s)
Guideline for the Management of HAE (2017)[14]	• Recommended treatment options for HAE attacks include C1-INH, ecallantide, or icatibant. • Intubation or tracheotomy should be considered early in progressive upper airway edema. • All patients should have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times. Short-term and Pre-procedural Prophylaxis • The administration of short-term prophylaxis should be considered before procedures that can induce an attack (all medical, surgical and dental procedures associated with any mechanical impact to the upper aerodigestive tract). Long-term Prophylaxis • Prophylaxis should be considered for patients who face events in life that are associated with increased disease activity. • Evaluating patients for long-term prophylaxis at every visit is recommended. Disease burden and patient preference should be taken into consideration. • C1-Inhibitor is recommended for first line long term prophylaxis. • Androgens are recommended as second-line long-term prophylaxis. • Adaptation of long-term prophylaxis in terms of dosage and/or treatment interval is suggested as needed to minimize burden of disease. Management of HAE Type I and II in Children • Testing children from HAE-affected families should be done as soon as possible and all offspring of an affected parent be tested. • C1-INH treatment is recommended for HAE attacks in children under the age of 12. • The indications for long-term prophylaxis in adolescents are the same as in adults. The preferred therapy for long-term prophylaxis is pdC1-INH. Management of HAE Type I and II During Pregnancy and Lactation • During pregnancy and lactation, C1-INH is the preferred therapy for HAE attacks. Home Therapy and Self-administration • It is recommended that all patients have an action plan. • HAE-specific comprehensive, integrated care should be available for all patients. • It is recommended that all patients who are provided with on-demand treatment that is licensed for self-administration should be taught to self-administer. • All patients with HAE should be educated about possible triggers which may induce HAE attacks.
United States Hereditary Angioedema Association Medical Advisory Board: **Guidelines for the Management of Hereditary Angioedema (2020)**[15]	On-demand Treatment • Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. • An FDA-approved on-demand HAE medication (ecallantide, icatibant, pdC1INH, or recombinant C1-INH) should be used as first-line treatment for attacks whenever possible. • On-demand treatment of HAE attacks should be self-administered (or administered by a caregiver) whenever feasible except when treating with ecallantide that needs to be administered by a health care provider. • All HAE attacks are eligible for treatment irrespective of the location of the swelling or the severity of the attack. Prophylactic Treatment

Clinical Guideline	Recommendation(s)
	• Short-term prophylaxis is indicated when patients are at increased risk of having an attack associated with known triggers such as invasive dental or medical procedures or stressful life events. • The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. • Long-term prophylactic treatment of HAE due to C1-INH deficiency should include first-line medication (intravenously administered C1-INH, subcutaneously administered C1-INH, or lanadelumab-flyo). • Progestin-only medication or an antifibrinolytic drug should be considered for initial long-term prophylactic treatment of HAE with normal C1-INH. <u>Additional Considerations for Children</u> • HAE due to C1-INH deficiency often presents in childhood and an early diagnosis is essential for minimizing the risks of morbidity and mortality. • Indications for the use of first-line HAE medications are the same in children as in adults, although regulatory differences affect the use of some medications depending on the child's age. <u>Specific Issues in the Management of HAE in Women</u> • Exogenous estrogens such as birth control pills or hormonal replacement therapy can precipitate HAE attacks and should therefore be used only with caution in individuals with HAE. • During pregnancy and breast-feeding, C1-INH is the recommended HAE medication for use as either on-demand or prophylactic therapy. <u>Management Plans</u> • HAE management plans must be individualized to each patient's needs due to wide variability in HAE symptoms, response to and tolerance of various HAE medications, and numerous factors impacting clinical course and quality of life. • Treatment plans should be monitored regularly and adjusted based on the needs of the patient. • HAE management plans should include: o Effective on-demand medication for every patient o Consideration of long-term prophylactic medications to prevent HAE attacks o Use of short-term prophylactic medications before medical procedures or other events known to trigger HAE symptoms • Consultation with an HAE expert physician is recommended to optimize individualized treatment plans, assist with coordination of care, and provide important patient and family education. • Patients should maintain a symptom/treatment diary to monitor angioedema symptoms, medication requirements and any adverse effects of treatment. o These data should be reviewed regularly at follow-up visits. <u>Burden of Illness</u> • Clinicians should explicitly consider the impact of HAE on their patients' lives. • Management plans should be individualized to lessen the burden of illness and provide patients with HAE with a normal quality of life. • Economic considerations should not be the determining factor in deciding the physician's recommendations for optimal management of HAE.
International Collaboration in Asthma, Allergy, and Immunology (iCAALL):	<u>Treatment of Attacks</u> • Approved treatments for attacks (i.e., plasma-derived nanofiltered C1-INH, icatibant) are efficacious and safe for on-demand treatment and are most effective when administered early in an attack. • Fresh frozen plasma should be used to treat attacks of HAE when no other

Clinical Guideline	Recommendation(s)
International consensus on hereditary and acquired angioedema (2012)[16]	treatment proven to be effective is available. • Fresh frozen plasma is generally effective in treating acute attacks of angioedema; however, sometimes it lacks efficacy or can cause sudden worsening of symptoms. ○ Fresh frozen plasma also carries a risk of viral transmission. Long-term Prophylaxis • Patients not treated successfully with on-demand therapy should be considered for long-term prophylaxis. • Attack frequency and severity, location of and access to acute care, other comorbid conditions, individual circumstances, and patient values and preferences may all influence the decision to undergo treatment with long-term prophylaxis. • In addition to being efficacious for on-demand treatment of attacks, pdC1-INH has also been reported to be effective for long-term prophylaxis. • The additional agents that can be used for long-term prophylaxis include 17α-alkylated androgens, danazol, stanozolol, oxandrolone, antifibrinolytics. Short-term Prophylaxis • Short-term prophylaxis can be achieved with administration of pdC1-INH or, if pdC1-INH is not available, infusion of solvent or detergent-treated plasma or fresh frozen plasma several (up to six) hours before a scheduled procedure. • High-dose 17α-alkylated androgens taken for five to seven days before and two days after the procedure is an alternative strategy for short-term prophylaxis. • For emergency procedures and in pregnant patients, administration of pdC1-INH is preferred. • A dose of on-demand short-term treatment drug (C1-INH, ecallantide, or icatibant) should be readily available, particularly for dental procedures or surgical procedures that require intubation. • In selected situations (e.g., when trauma is expected to be minimal and on-demand therapy is readily available), omission of preprocedural treatment with on-demand treatment contingent on any signs of an attack is an alternative management approach. Treatment in Special Groups: Children, Women, and Pregnant Women • Changes in estrogen in association with puberty, menopause, or hormone replacement therapy, oral contraceptive use, or pregnancy can provoke or exacerbate a tendency for more frequent and/or severe attacks in some women with C1-INH deficiency. • For pregnant patients with more serious flares of HAE, long-term prophylaxis is an appropriate intervention because the potential for benefit exceeds the potential for harm and burden associated with this treatment. • The decision to prescribe long-term prophylaxis during pregnancy should be considered carefully on an individualized basis and involve the patient in the decision-making process. • Because treatment with androgens is contraindicated during pregnancy, pdC1-INH is preferred and may also be considered for women desiring to become pregnant. • Angioedema attacks during labor and delivery are relatively rare and can be managed expectantly by having an on-demand HAE-specific agent available should an episode of angioedema occur. • Clinical trials investigating the efficacy and safety of novel agents for children are lacking; however, clinical experience with C1-INH replacement therapy in children implies these agents are favorable from the standpoint of balancing the

Clinical Guideline	Recommendation(s)
	potential for benefit with the potential for harm or burden in properly selected patients.

C1-INH=C1 esterase inhibitor, HAE=hereditary angioedema, pdC1-INH=plasma-derived C1 esterase inhibitor (Berinert®, Cinryze®, and Haegarda®)

III. Indications

The Food and Drug Administration (FDA)-approved indications for the complement inhibitors for the treatment of hereditary angioedema are noted in Table 3.

Table 3. FDA-Approved Indications for the Complement Inhibitors for the Treatment of HAE[3-11]

Indication	Berotralstat hydrochloride (Orladeyo®)	C1 Esterase Inhibitor, Human (Berinert®)	C1 Esterase Inhibitor, Human (Cinryze®)	C1 Esterase Inhibitor, Human (Haegarda®)	C1 Esterase Inhibitor, Recombinant (Ruconest®)	Icatibant (Firazyr®)	Lanadelumab -flyo (Takhzyro®)
Prophylaxis to prevent attacks of HAE in patients 12 years and older	✔						✔
Routine prophylaxis to prevent HAE attacks in patients 6 years of age and older				✔			
Routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (≥6 years of age) with HAE			✔				
Treatment of acute attacks in adult and adolescent patients with HAE					✔ *		
Treatment of acute attacks of HAE in adults 18 years of age and older						✔	
Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients		✔					

* Effectiveness not established in HAE patients with laryngeal attacks
HAE=hereditary angioedema

IV. Pharmacokinetics

The pharmacokinetic parameters of the complement inhibitors for the treatment of hereditary angioedema are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Complement Inhibitors for the Treatment of HAE[11]

Generic Name(s)	Bioavailability (%)	Time to Peak Concentration	Half-Life
Berotralstat hydrochloride	Not reported	5 hours	93 hours
C1 esterase inhibitor, human	100 (IV*)	3.9 hours (IV*)	32.7 to 56 hours (IV*)
	42.7 (SC†)	59 hours (SC†)	69 hours (SC†)
C1 esterase inhibitor, recombinant	100	0.31 hours	2.4 to 2.7 hours
Icatibant	97	0.75 hours	1.4 hours
Lanadelumab-flyo	Not reported	4.11 to 5.17 days	14.2 to 15 days

*IV products=Berinert® and Cinryze®
†SC product=Haegarda®
IV=intervenous, SC=subcutaneous

V. Drug Interactions

Significant drug interactions with the complement inhibitors for the treatment of hereditary angioedema are listed in Table 5.

Table 5. Significant Drug Interactions with the Complement Inhibitors for the Treatment of HAE[3-11]

Generic Name(s)	Interaction	Mechanism
Berotralstat hydrochloride	BCRP inhibitors	Concomitant use of berotralstat and BCRP inhibitors may result in increased berotralstat exposure.
Berotralstat hydrochloride	CYP2D6 substrates (e.g., thioridazine, pimozide)	Concomitant use of berotralstat and CYP2D6 substrates with a narrow therapeutic index (e.g., thioridazine, pimozide) may result in increased CYP2D6 substrate exposure. Appropriate monitoring and dose titration is recommended.
Berotralstat hydrochloride	CYP3A4 substrates	Concomitant use of berotralstat and CYP3A substrates with a narrow therapeutic index may result in increased CYP3A substrate exposure. Appropriate monitoring and dose titration is recommended.
Berotralstat hydrochloride	digoxin	Concomitant use of berotralstat and digoxin may result in increased digoxin exposure. Monitor serum digoxin concentrations and titrate dose as needed.
Berotralstat hydrochloride	P-gp inducers/ inhibitors	Concomitant use of berotralstat and P-gp inducers/inhibitors may result in increased berotralstat exposure.
Icatibant	ACE inhibitors	Concomitant use of an ACE inhibitor with icatibant may reduce the antihypertensive effect of the ACE inhibitor. Consider monitoring for lack of blood pressure control when coadministered.

ACE=angiotensin-converting enzyme, BCRP=breast cancer resistance protein, P-gp=P-glycoprotein

VI. Adverse Drug Events

The most common adverse drug events reported with the complement inhibitors for the treatment of hereditary angioedema are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Complement Inhibitors for the Treatment of HAE[3-11]

Adverse Event(s)	Berotralstat hydrochloride	C1 Esterase Inhibitor, Human	C1 Esterase Inhibitor, Recombinant	Icatibant	Lanadelumab-flyo
Gastrointestinal					
Abdominal pain	10 to 23	≤5	✔	-	-
Diarrhea	10 to 15	✔	2	-	≤4
Gastroesophageal reflux disease	5 to 10	-	-	-	-
Nausea	-	≤18	2	✔	-
Vomiting	10 to 15	≤10	-	-	-
Administration Conditions					
Anaphylaxis	-	✔	✔	-	-
Angioedema	-	≤4	≤3	-	-
Antibody development	-	≤28	1 to 10	4	12
Burning sensation of skin	-	-	≤2	-	-
Chills	-	✔	-	-	-
Erythema	-	2	≤2	-	-
Fever	-	5	-	4	-
Hypersensitivity	-	≤7	✔	-	1
Infusion reaction	-	✔*	-	-	-
Injection site reaction	-	≤35	-	97	45 to 56
Pruritus	-	≤8	-	-	-
Rash	<1	≤21	✔	✔	4 to 10
Shock	-	✔	-	-	-
Swelling	-	<4	-	-	-
Urticaria	-	✔	-	-	-
Investigations					
Transaminase increased	✔	-	-	4	4
Nervous System Disorders					
Dizziness	-	≤9	-	3	4 to 10
Headache	9	≤19	≤10	✔	21 to 33
Procedural Headache	-	-	≤2	-	-
Vertigo	-	-	≤3	-	-
Other					
Back pain	2 to 10	-	≤3	-	-
Bronchitis	-	-	-	-	-
C-reactive protein increased	-	-	≤2	-	-
Catheter site pain	-	3*	-	-	-
Cerebrovascular accident	-	<1	-	-	-
Deep vein thrombosis	-	<3	-	-	-
Dysgeusia	-	5	-	-	-
Fatigue	6	-	-	-	-
Flatulence	6	-	-	-	-
Increased fibrin	-	-	≤2	-	-
Influenza like illness	-	≤4	-	-	-
Laryngeal edema	-	≤4	-	-	-
Laryngospasm	-	≤4	-	-	-
Lipoma	-	-	≤2	-	-
Myalgia	-	-	-	-	≤11
Nasopharyngitis	-	≤19	-	-	-
Sneezing	-	-	≤2	-	-
Swelling	-	≤4	-	-	-
Thrombosis/Thromboembolism	-	✔	✔	-	-
Upper respiratory tract infection	-	≤2	-	-	31 to 44
Vulvovaginal mycotic infection	-	≤4	-	-	-

* Intervenous only.
✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the complement inhibitors for the treatment of hereditary angioedema are listed in Table 7.

Table 7. Usual Dosing Regimens for the Complement Inhibitors for the Treatment of HAE[3-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Berotralstat hydrochloride (Orladeyo®)	Routine prophylaxis to prevent HAE attacks in adult patients: Oral capsule: 150 mg once daily; maximum 150 mg once daily	Routine prophylaxis to prevent HAE attacks in patients ≥12 years of age: Oral capsule: 150 mg once daily; maximum 150 mg once daily Safety and efficacy have not been established in children <12 years of age.	Oral capsule: 110 mg 150 mg
C1 esterase inhibitor, human (Berinert®)	Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult patients: IV injection: initial, 20 IU/kg IV; maximum, 20 IU/kg IV	Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adolescent and pediatric patients: IV injection: initial, 20 IU/kg IV; maximum, 20 IU/kg IV	IV injection: 500 U (single-use vial)
C1 esterase inhibitor, human (Cinryze®)	Routine prophylaxis against angioedema attacks in adult patients with HAE: IV injection: initial, 1,000 U IV every three or four days; maximum, 2,500 U IV (not to exceeded 100 U/kg) every three or four days	Routine prophylaxis against angioedema attacks in adolescent and pediatric patients (6 years of age and older) with HAE: IV injection, patients ≥12 years of age: initial, 1,000 U IV every three or four days; maximum, 2,500 U IV (not to exceeded 100 U/kg) every three or four days IV injection, patients six to 11 years of age: initial, 500 U IV every three or four days; maximum, 1,000 U IV every three or four days	IV injection: 500 U (single-use vial)
C1 esterase inhibitor, human (Haegarda®)	Routine prophylaxis to prevent HAE attacks in adult patients: SC injection: initial, 60 IU/kg SC twice weekly (every three or four days); maximum, 60 IU/kg SC twice weekly (every three or four days	Routine prophylaxis to prevent HAE attacks in adolescent patients: SC injection: initial, 60 IU/kg SC twice weekly (every three or four days); maximum, 60 IU/kg SC twice weekly (every three or four days Safety and efficacy have not been established in children <12 years of age.	SC injection: 2,000 U 3,000 U

C1 esterase inhibitor, recombinant (Ruconest®)	Treatment of acute attacks of HAE in adults patients: IV injection: initial, 50 U/kg (<84 kg) or 4200 U (≥84 kg), may repeat once if symptoms persist; maximum 4200 U per dose, do not exceed two doses in 24 hours	Treatment of acute attacks of HAE in adolescent patients: IV injection: initial, 50 U/kg (<84 kg) or 4200 U (≥84 kg), may repeat once if symptoms persist; maximum 4200 U per dose, do not exceed two doses in 24 hours Safety and efficacy have not been established in children <13 years of age.	IV injection: 2,100 U
Icatibant (Firazyr®)	Treatment of acute attacks of HAE in adults: SC injection: initial, 30 mg SC in the abdominal area, if response is inadequate or symptoms recur, additional 30 mg SC injections may be administered at intervals ≥6 hours; maximum, three injections per 24 hours	Safety and efficacy have not been established in patients <18 years of age.	SC injection: 10 mg/mL (3 mL single-use, prefilled syringe)
Lanadelumab-flyo (Takhzyro®)	Routine prophylaxis to prevent HAE attacks in adult patients: SC injection: initial, 300 mg every two weeks; 300 mg every four weeks may be considered if the patient is well-controlled (e.g., attack free) for more than six months	Routine prophylaxis to prevent HAE attacks in patients ≥12 years of age: SC injection: initial, 300 mg every two weeks; 300 mg every four weeks may be considered if the patient is well-controlled (e.g., attack free) for more than six months	SC injection: 300 mg/ 2 mL (single-use vial)

HAE=hereditary angioedema, IV=intravenous, SC=subcutaneous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the complement inhibitors for the treatment of hereditary angioedema are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Complement Inhibitors for the Treatment of HAE

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prophylaxis of Hereditary Angioedema				
Zuraw et al.[17] (2021) APeX-2 Berotralstat hydrochloride (Orladeyo®) 150 mg once daily vs berotralstat hydrochloride (Orladeyo®) 110 mg once daily vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a confirmed diagnosis of type I or II HAE and history of two or more investigator-confirmed HAE attacks within 56 days after the screening visit	N=121 24 weeks	Primary: Rate of investigator-confirmed HAE Attacks Secondary: Change from baseline in Angioedema Quality of Life questionnaire total scores, number and proportion of days with angioedema symptoms, rate of expert-confirmed angioedema attacks during dosing in the effective treatment period (steady state, beginning on day 8)	Primary: Berotralstat hydrochloride demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks per month; P=0.024) and 150 mg (1.31 attacks per month; P<0.001) relative to placebo (2.35 attacks per month). Secondary: With respect to change from baseline in Angioedema Quality of Life questionnaire total scores, the least squares mean difference from placebo was -2.77 (95% CI: -10.08 to 4.53) points in the 110 mg dose group (P=0.453) and -4.90 (95% CI: -12.23 to 2.43) points in the 150 mg dose group (P=0.188). The mean numbers of days with angioedema symptoms were 20.8 (±19.22), 19.4 (±21.50), and 29.2 (±24.29) days for the 110 mg dose, 150 mg dose, and placebo groups, respectively. The least squares mean differences from placebo in proportion of days with angioedema symptoms were -0.062 days (95% CI: -0.117 to -0.008) in the 110 mg dose group and -0.078 (95% CI: -0.133 to -0.023) in the 150-mg dose group. The investigator-confirmed attack rates were 1.65, 1.27, and 2.38 attacks per month in the 110 mg dose, 150-mg dose, and placebo groups, respectively.
Wedner et al.[18] (2021) APeX-2 Berotralstat hydrochloride (Orladeyo®) 150 mg once daily	ES of DB, MC, PC, PG, RCT Patients ≥12 years of age with a confirmed diagnosis of type I or II HAE and history of two or more	N=81 48 weeks	Primary: Number and proportion of subjects with treatment-emergent adverse events; discontinuations due to treatment-emergent adverse events, serious	Primary: Treatment-emergent adverse events were reported by 76 patients (94%) who were randomized to berotralstat hydrochloride. Seven patients (8.6%) receiving berotralstat hydrochloride discontinued treatment due to treatment-emergent adverse events. Two patients (2.5%) receiving berotralstat hydrochloride experienced serious treatment-emergent adverse events. Eight patients (9.9%) experienced grade 3 or 4 treatment-emergent adverse events or laboratory abnormalities. Two patients (2.5%) receiving berotralstat hydrochloride experienced investigator-identified rash.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs berotralstat hydrochloride (Orladeyo®) 110 mg once daily vs placebo	investigator-confirmed HAE attacks within 56 days after the screening visit who were randomized to berotralstat hydrochloride in both parts I and II of APeX-2.		treatment-emergent adverse events, grade 3 or 4 treatment-emergent adverse events or laboratory abnormalities, rash Secondary: Number and rate of investigator-confirmed HAE attacks, durability of response (attack rate trend over time), discontinuations due to lack of efficacy, durability of changes in Angioedema Quality of Life questionnaire	Secondary: Mean (standard error of the mean) monthly attack rates at baseline and week 48 were 3.06 (±0.25) and 1.06 (±0.25) in the berotralstat hydrochloride 150 mg group and 2.97 (±0.21) and 1.35 (±0.33) in the berotralstat hydrochloride 110 mg group. Ten patients (12.3%) discontinued berotralstat hydrochloride due to lack of efficacy. Patients experienced an improvement in the Angioedema Quality of Life total score, starting as early as week 4, which was sustained through week 48.
Oshawa et al.[19] (2021) APeX-J Berotralstat hydrochloride (Orladeyo®) 150 mg once daily vs berotralstat hydrochloride	DB, MC, PC, PG, RCT Patients ≥12 years of age with a confirmed diagnosis of type I or II HAE and history of two or more investigator-confirmed HAE attacks within 56 days after the	N=19 24 weeks	Primary: Rate of expert-confirmed angioedema attacks Secondary: Number and proportion of days with angioedema symptoms, rate of expert-confirmed angioedema attacks during dosing in the effective treatment	Primary: Treatment with berotralstat hydrochloride 150 mg significantly reduced HAE attacks relative to placebo (1.11 vs 2.18 attacks/month, P=0.003). Treatment with berotralstat hydrochloride 110 mg did not significantly reduce HAE attacks relative to placebo (1.64 vs 2.18, P=0.181). Secondary: The proportion of days with angioedema symptoms was not statistically significant for the 150 mg dose; therefore, statistical testing on the remaining secondary endpoints was stopped. Reductions in expert-confirmed HAE attack rates over the effective treatment period (steady state, day 8 to week 24) relative to placebo were 25% and 48% for the 110 mg and 150 mg groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Orladeyo®) 110 mg once daily vs placebo	screening visit		period (steady state, beginning on day 8), change from baseline in quality of life as assessed by the Angioedema Quality of Life questionnaire	The least-squares mean difference from placebo in Angioedema Quality of Life questionnaire scores was -12.7 and -19.0 for the 110 mg and 150 mg groups, respectively.
Zuraw et al.[20] (2010) C1-INH (Cinryze®) 1,000 U IV twice weekly vs placebo OL C1-INH injections were allowed as rescue therapy.	DB, PC, PRO, RCT, XO Patients ≥6 years of age with a confirmed diagnosis of HAE and history ≥2 attacks per month	N=22 24 weeks	Primary: Average number of attacks Secondary: Average severity of attacks, average duration of attacks, number of OL injections of C1-INH, and total number of days of swelling	Primary: The average number of attacks was significantly lower with C1-INH compared to placebo (6.26 vs 12.73 attacks; treatment difference, 6.47 attacks; 95% CI, 4.21 to 8.73; P<0.0001). Secondary: The average score for severity (three point scale) of attacks was significantly lower with C1-INH compared to placebo (mean±standard deviation, 1.30±0.85 vs 1.90±0.36; P<0.0001). The total duration of attacks was significantly shorter with C1-INH compared to placebo (mean±standard deviation, 2.10±1.13 vs 3.40±1.39 days; P=0.002). A total of 11 and 22 patients receiving C1-INH and placebo, respectively, required OL rescue therapy. C1-INH therapy was associated with significantly fewer OL injections (mean±standard deviation, 4.70±8.66 vs 15.40±8.41 injections; P<0.001) and days of swelling (mean±standard deviation, 10.10±10.73 vs 29.6±16.9 days; P<0.001) compared to placebo.
Longhurst et al.[21] (2017) COMPACT CSL830 (Haegarda®) 40 IU/kg SC twice weekly vs	DB, MC, PC, PRO, RCT, XO Patients ≥12 years of age with a confirmed diagnosis of type I or II HAE who experienced ≥4 qualifying attacks over a	N=90 40 weeks	Primary: The number of attacks of angioedema Secondary: The percentage of patients with response, the mean use of rescue medication per	Primary: The mean difference, as compared to placebo, in the number of attacks of angioedema per month was -2.42 (95% CI, -3.38 to -1.46; P<0.001) with 40 IU/kg and -3.51 (95% CI, -4.21 to -2.81; P<0.001) with 60 IU/kg. There was no significant difference between the 40-IU and 60-IU treatment sequences. Secondary: The percentage of patients with response (≥50% reduction in attacks compared to placebo) was 76% (95% CI, 62% to 87%) with 40 IU/kg and 90% (95% CI, 77% to 96%) with 60 IU/kg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CSL830 (Haegarda®) 60 IU/kg SC twice weekly vs placebo	two month period and who did not receive routine prophylaxis with an IV C1-INH inhibitor within three months before screening		month, and adverse effects	The mean difference, as compared to placebo, in the use of rescue medication per month was -4.42 (95% CI, -8.03 to -0.81; P=0.02) with 40 IU/kg and -3.57 (95% CI, -4.50 to -2.64; P<0.001) with 60 IU/kg. The percentage of patients experiencing adverse events were similar between both CSL830 treatment groups and placebo with 67%, 70%, and 66% of patients experiencing an adverse event with 40 IU/kg, 60 IU/kg, and placebo, respectively.
Levy et al.[22] (2020) COMPACT C1-INH (Haegarda®) 40 IU/kg SC twice weekly vs C1-INH (Haegarda®) 60 IU/kg SC twice weekly vs placebo	ES, OL of DB, MC, PC, PG, RCT Patients ≥6 and ≤17 years of age with a confirmed diagnosis of type I or II HAE who experienced ≥4 qualifying attacks over a consecutive two-month period before enrollment in the OL ES or the PC COMPACT trial	N=10 52 to 140 weeks	Primary: Long-term safety Secondary: Percentage of responders (≥50% reduction in attacks compared with the prestudy period), percentage of subjects with <1 HAE attack per 4-week period	Primary: Injection-site reactions occurred in three patients (30%) and were the most common adverse event. No pediatric subject discontinued treatment due to a treatment-related adverse event. There were no reports of serious adverse events, thromboembolism, or anaphylaxis. Secondary: All ten patients (100%) were classified as responders (≥50% reduction in attacks compared with the pre-study period). All ten patients (100%) experienced <1 HAE attack per 4-week period during C1-INH treatment.
Bernstein et al.[23] (2020) COMPACT C1-INH (Haegarda®) 40 IU/kg SC twice weekly	ES, OL of DB, MC, PC, PG, RCT Patients ≥65 years of age with a confirmed diagnosis of type I or II HAE who	N=10 52 to 140 weeks	Primary: Person-time incidence rates of related serious adverse events, adverse events leading to premature discontinuation, adverse events of	Primary: Two patients (20%) experienced serious adverse events but the events resolved and did not lead to discontinuation. There were no treatment-related thromboembolic events or reports of anaphylaxis in any patients. One patient (10%) experienced a HAE attack resulting in hospitalization. Local injection site reactions were the most common adverse events and occurred in five patients (50%). Specific adverse events occurring in more than one patient included: injection site bruising (N=2, related), injection site pain (N=2, related), urinary tract infection (N=2, unrelated), and diarrhea (N=2, unrelated).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs C1-INH (Haegarda®) 60 IU/kg SC twice weekly vs placebo	experienced ≥4 qualifying attacks over a consecutive two-month period before enrollment in the OL ES or the PC COMPACT trial		special interest (e.g., thromboembolic events, anaphylaxis), HAE attacks resulting in hospitalization Secondary: Percentage of responders (≥50% reduction in attacks compared with the prestudy period), percentage of subjects with <1 HAE attack per 4-week period	Secondary: Six patients (60%) were classified as responders (≥50% reduction in attacks compared with the prestudy period). Six patients (60%) experienced <1 HAE attack per 4-week period during C1-INH treatment.
Banerji et al.[24] (2018) HELP Lanadelumab-flyo 150 mg every four weeks vs lanadelumab-flyo 300 mg every four weeks vs lanadelumab-flyo 300 mg every two weeks	DB, MC, PG, RCT Patients ≥12 years of age with type I or II HAE who experienced at least one investigator-confirmed HAE attack per four weeks during the run-in period	N=125 26 weeks	Primary: Mean attack rate Secondary: Mean HAE attacks requiring acute treatment, mean moderate to severe attack rate	Primary: The mean attack rate was significantly lower in the three lanadelumab-flyo treatment groups at 0.48, 0.53, and 0.26, respectively compared to placebo at 1.97 (P<0.001 for all comparisons). Secondary: The mean number of HAE attacks requiring acute treatment from day 0 to 182 was also significantly lower in the three lanadelumab-flyo treatment groups at 0.31, 0.42, and 0.21, respectively compared to placebo at 1.64 (P<0.001 for all comparisons). The mean number of moderate to severe attacks from day 0 to 182 was significantly lower in the three lanadelumab-flyo treatment groups at 0.36, 0.32, and 0.20, respectively compared to placebo at 1.22 (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Lumry et al.[25] (2021) HELP Lanadelumab-flyo 150 mg every four weeks vs lanadelumab-flyo 300 mg every four weeks vs lanadelumab-flyo 300 mg every two weeks vs placebo	DB, MC, PG, RCT Patients ≥12 years of age with type I or II HAE who experienced at least one investigator-confirmed HAE attack per four weeks during the run-in period	N=125 26 weeks	Primary: Angioedema Quality of Life Questionnaire	Primary: Compared with the placebo group, the lanadelumab-flyo total group demonstrated significantly greater improvements in Angioedema Quality of Life questionnaire total and domain scores (mean change, -13.0 to -29.3; P<0.05 for all); the largest improvement was in functioning. A significantly greater proportion of the lanadelumab-flyo total group achieved the minimal clinically important difference (70% vs 37%; P=0.001).
Reidl et al.[26] (2020) HELP Lanadelumab-flyo 150 mg every four weeks vs lanadelumab-	Post-hoc analysis of DB, MC, PG, RCT Patients ≥12 years of age with type I or II HAE who experienced at least one investigator-confirmed HAE	N=125 26 weeks	Primary: Least-squares mean monthly HAE attack rate for days 0 to 69	Primary: The mean monthly attack rate was significantly lower with lanadelumab-flyo (0.41 to 0.76) vs placebo (2.04), including attacks requiring acute treatment (0.33 to 0.61 vs 1.66) and moderate/severe attacks (0.31 to 0.48 vs 1.33, all P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flyo 300 mg every four weeks vs lanadelumab-flyo 300 mg every two weeks vs placebo	attack per four weeks during run-in period			
Treatment of Acute Hereditary Angioedema				
Craig et al.[27] (2010) I.M.P.A.C.T.2 C1-INH (Berinert®) 20 U/kg IV once for each attack	ES, OL, MC, PRO Patients ≥6 years of age with a confirmed diagnosis of type I or II HAE with an active laryngeal attack	N=16 4 years	Primary: Time to onset of symptom relief Secondary: Time to complete resolution of all symptoms	Primary: Median time to onset of symptom relief was 0.25 hours for the 30 attacks; all attacks were treated successfully. Median time to onset of relief for individual mean values per patient was 0.44 hours. Within one hour after administration, onset of relief was reported in ≥95% of all attacks, and the time to onset of relief was ≤0.75 hours in ≥85% of patients. Secondary: Median time to complete resolution of all symptoms was 8.25 hours when analyzed by attack and 5.87 hours when analyzed as the mean value per patient. Time to complete resolution of all symptoms was <16 hours in 75% of patients and <24 hours in 74% of attacks.
Craig et al.[28] (2011) I.M.P.A.C.T.2 C1-INH (Berinert®) 20 U/kg IV once for each attack	ES, OL, MC, PRO Patients ≥6 years of age with a confirmed diagnosis of type I or II HAE with an active attack	N=57 4.5 years; median duration of follow-up, 24 months	Primary: Time to onset of symptom relief Secondary: Time to complete resolution of all symptoms	Primary: Median time to onset of symptom relief was 0.46 hours. The individual average time was <1 hours in 89.5% of patients. Median times to onset of symptom relief were comparable for all types of attacks (range, 0.39 to 0.48 hours). Secondary: Median time to complete symptom resolution was 15.5 hours. The individual average time was <24 hours in 71.9% of patients. Median time to complete resolution of symptoms was shortest for laryngeal attacks. A single dose effectively treated 99% (1,073/1,085) of HAE attacks. Additional doses were administered for 12 abdominal attacks in six patients for worsening of the attacks or because the patients felt the attack did not resolve quickly enough.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				None of the attacks treated with additional doses of C1-INH concentrate were associated with adverse drug reactions.
Bork et al.[29] (2001) C1-INH (Berinert®) 500 to 1,000 U IV	Case series Patients with a confirmed diagnosis type I or II HAE experiencing typical clinical symptoms of HAE	N=95 Patients were enrolled over a 20 year period	Primary: Time from injection to the first signs of symptom resolution Secondary: Time from injection to the end of symptom progression	Primary: The interval from injection to interruption in progress of symptoms ranged from 10 minutes to four hours (mean±standard deviation, 42.2±19.9 minutes). In all patients, difficulty breathing and fear of asphyxiation were the first symptoms that resolved. Dysphagia, the sensation of a lump in the throat and voice changes took longer to resolve completely. All patients experienced the onset of relief within four hours after C1-INH administration. Secondary: The mean duration of laryngeal edema was 15.3 hours (standard deviation, ±9.3 hours) in patients receiving C1-INH compared to 100.8 hours (standard deviation, ±26.2 hours) in patients who received no treatment (P<0.001).
Craig et al.[30] (2009) I.M.P.A.C.T.1 C1-INH (Berinert®) 10 U/kg IV once vs C1-INH (Berinert®) 20 U/kg IV once vs placebo Patients, initially receiving C1-INH 10 U/kg or placebo who	DB, MC, PC, PG, PRO, RCT Patients ≥6 years of age with a confirmed diagnosis type I or II HAE with an acute moderate-to-severe abdominal or facial attack within five hours of the attack attaining moderate intensity	N=125 24 hours Single attack trial	Primary: Time to onset of symptom relief Secondary: Time to complete HAE symptom resolution, proportion of patients with worsened intensity of HAE symptoms between two and four hours after start of treatment, number of vomiting episodes within four hours of start of treatment, and safety	Primary: Median time to onset of symptom relief was significantly shorter with C1-INH 20 U/kg compared to placebo (0.5 vs 1.5 hours; P=0.0025). There was no significant difference between C1-INH 10 U/kg and placebo treatments (1.2 vs 1.5 hours; P=0.2731). Secondary: Median time to complete HAE symptom resolution was significantly shorter with C1-INH 20 U/kg compared to placebo (4.9 vs 7.8 hours; P=0.0237). The median time was longer with C1-INH 10 U/kg compared to placebo (P value not reported). The proportion of patients with worsened intensity of HAE symptoms between two and four hours after the start of treatment was significantly lower with C1-INH 20 U/kg compared to placebo (4.7 vs 31.0%; P=0.0014). The mean number of vomiting episodes within four hours after start of treatment was significantly lower with C1-INH 20 U/kg compared to placebo (0.1 vs 0.8; P=0.0329). The proportion of patients experiencing an adverse event within four hours of the start of treatment was lower with C1-INH 20 U/kg compared to placebo (19.6 vs 43.9%; P value not reported). The most frequently reported adverse events were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
reported an inadequate response after four hours were eligible to receive another 10 U/kg dose (active group) or 20 U/kg dose (placebo group).				nausea, diarrhea, abdominal pain and muscle spasms. The frequencies of these events were lower with C1-INH 20 U/kg compared to placebo.
Zuraw et al.[31] (2010) C1-INH (Cinryze®) 1,000 U administered IV once or twice vs placebo	DB, PC, PRO, RCT Patients ≥6 years of age with confirmed diagnosis of HAE presenting within four hours of an acute attack	N=68 Single attack trial	Primary: Time to onset of unequivocal relief Secondary: Proportion of patients who had an onset of unequivocal relief within four hours, time to complete resolution of the attack and effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels	Primary: Time to onset of unequivocal relief was significantly shorter with C1-INH compared to placebo (two vs four hours; estimated success rate ratio, 2.41; 95% CI, 1.17 to 4.95; P=0.02). Secondary: There was no significant difference in the proportion of patients achieving onset of unequivocal relief within four hours between the C1-INH and placebo treatment groups (60 vs 44%, respectively; P=0.06). A second dose of blinded study drug was administered in 23 and 28 patients randomized to C1-INH and placebo, respectively. The median time to complete resolution of symptoms was significantly shorter with C1-INH compared to placebo (12.3 vs 25.0 hours; P=0.004), even though all patients who did not have substantial improvement by the end of the four hour assessment period were given OL C1-INH. Both antigenic and functional levels of C1 inhibitor increased significantly with C1-INH (P<0.001 for both). In contrast, C4 levels did not change and were not different between the two treatments (P=0.86).
Kunschak et al.[32] (1998) C1-INH 25 PU/kg IV once vs	DB, PC, PRO, RCT Patients with HAE presenting within five hours of an attack with	N=23 Single attack trial	Primary: Time to relief Secondary: Time to resolution	Primary: Time to relief was significantly shorter with C1-INH compared to placebo (7.62 vs 15.35 hours; P=0.007). Secondary: There was no significant difference between the two treatments with time to resolution of symptoms (23.98 vs 34.58 hours; P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo OL treatment with C1-INH was allowed in severe cases based on predetermined criteria.	a history ≥5 attacks during the 12 months preceding the study and with a contraindication, adverse reaction, or inadequate response to androgen therapy			
Aberer et al.[33] (2014) EASSI Icatibant 30 mg SC self-administered All patients received training on administration technique, icatibant naïve patients also received the first dose administered by a HCP	MC, OL, PRO Patients ≥18 years of age with a confirmed diagnosis of type I or II HAE	N=97 21 months Single attack trial	Primary: Clinical safety of a self-administered dose for an acute HAE attack Secondary: Local tolerability of injection, patient convenience, and efficacy	Primary: A total of 34.0% of patients experienced at least one adverse event following icatibant self-administration and 50.0% experienced at least one adverse event following HCP-administration. The majority of events were mild or moderate with eight patients experiencing severe events (seven following self-administration and one following HCP-administration). The most common adverse event was worsening or recurrence of HAE symptoms within 48 hours of icatibant treatment, reported in 6 patients (27.2%) in HCP-administered phase and 22 (22.6%) patients in the self-administration phase. Secondary: Injection site reactions were reported by 96.9% of patients during the self-administration phase. Also in the self-administration phase, 17.5% of patients reported severe injection site reactions. None of these reactions required intervention. Based on treatment satisfaction questionnaire responses, the majority of patients were satisfied with the results of self-administered icatibant in terms of convenience and ease of use. Rescue medication was used by 33.3% of patients with worsening or recurrence of HAE symptoms during the HCP-administration phase and by 59.1% of patients with worsening or recurrence during the self-administration phase. The median time to the onset of symptom relief was 3.8 hours by three-symptom VAS and 2.0 hours by primary symptom VAS.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bork et al.[34] (2007) Icatibant 0.4 mg/kg IV administered over two hours (Group 1) vs icatibant 0.4 mg/kg IV administered over 30 minutes (Group 2) vs icatibant 0.8 mg/kg IV administered over 30 minutes (Group 3) vs icatibant 30 mg SC (Group 4) vs icatibant 45 mg SC (Group 5)	Uncontrolled, pilot trial Patients 18 to 65 years of age with documented HAE and a recent attack frequency ≥1 every three months, with the current attack being of moderate to severe intensity at any location excluding laryngeal edema	N=15 Single attack trial	Primary: Efficacy Secondary: Safety	Primary: Median time to onset of symptom relief was 1.50, 1.42 and 1.13 hours with IV therapy (12 attacks) and 0.58 and 0.45 hours with SC therapy (eight attacks). Overall, treatment resulted in a mean time to onset of symptom relief of 1.16hours (standard deviation, ±0.95 hours). Improvement of baseline symptoms after four hours was similar among the various groups, with median differences in the VAS scores of 5.31, 1.92 and 5.61 cm with IV therapy, and 3.15 and 4.31 cm with SC therapy. The median difference in the VAS score after four hours was 4.11 cm (95% CI, 1.72 to 6.07 cm; P<0.01) in all 15 patients. Historical data of a large number of attacks manifesting at the same location as the current attacks were available for all patients. Ten of 15 patients had >100 attacks before treatment. Unlike the short time to onset of symptom relief in all treated patients – (mean±standard deviation, 1.16±0.95 hours), the untreated attacks had a long time to onset of symptom relief (mean±standard deviation, 42.01±14.1 hours). Treatment led to a 97% reduction in the time to relief. Secondary: Among the skin swellings treated attacks, there were six facial swellings in five patients and 15 episodes of swellings in extremities in 12 patients. After onset of relief, there was no further increase or worsening of the skin swellings, and then the skin swelling continuously improved until it disappeared completely or until there was only a minimal residual swelling. The mean period between the maximum of skin swellings and the end of the swellings or the minimal residual swelling was 13.9hours (standard deviation, ±12.3 hours; range, 0.5 to 45.2 hours). All patients reported that all treated swellings were considerably shorter than usual. After SC administration, local reactions were noted in all patients, including itching, urticaria wheal, erythema and mild burning pain. Pain lasted for minutes, itching and urticaria wheal lasted for hours, and residual erythema cleared within 24 hours. All symptoms resolved spontaneously and did not require medical intervention. In none of the patients was the response severe enough that the patient would consider refusing therapy. One patient experienced moderate headache more than four hours after the infusion of icatibant. There were no other

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events assessed as related to the study drug. Plasma bradykinin was consistently increased as much as 30-fold above normal levels. Four hours after infusion, median bradykinin was decreased from 48.5 to 18.0 pmol/L. Four hours after SC administration, there was a nonsignificant decrease in bradykinin from 75.0 to 30.5 pmol/L (P value not reported).
Cicardi et al.[35] (2010) FAST-1 and -2 Icatibant 30 mg SC once vs placebo (FAST-1) or tranexamic acid 3 g/day for two days (FAST-2) Patients with life-threatening laryngeal angioedema were also treated with OL icatibant.	Two DB, MC, PRO, RCT Patients ≥18 years of age with documented HAE presenting with cutaneous or abdominal attacks	N=130 Single attack trial	Primary: Time to clinically significant relief of symptoms Secondary: Time to first symptom improvement according to the patient and according to the investigator, time to almost complete relief of symptoms, proportion of patients reaching the median time to clinically significant relief of the index symptom within four hours after the start of treatment, use of rescue medication and safety	Primary: Median time to clinically significant symptom relief was not different with icatibant compared to placebo (2.5 vs 4.6 hours; P=0.14). The median time to clinically significant symptom relief was significantly shorter with icatibant compared to tranexamic acid (2.0 vs 12.0 hours; P<0.001). Secondary: Median time to first symptom improvement was significantly shorter with icatibant compared to placebo, as assessed by patients (0.8 vs 16.9 hours; P<0.001) and by investigators (1.0 vs 5.7 hours; P<0.001). Similar results were observed with icatibant compared to tranexamic acid (0.8 vs 7.9 hours; P<0.001 and 1.5 vs 6.9 hours; P<0.001). Median time to almost complete relief of symptoms was not significantly different between icatibant and placebo (8.5 vs 19.4 hours; P=0.08); however, it was significantly shorter with icatibant compared to tranexamic acid (10.0 vs 51.0 hours; P<0.001). The proportion of patients with clinically significant relief of the index symptom after four hours was not different between icatibant and placebo (67 vs 46%, respectively; P=0.18); however, it was significantly larger with icatibant compared to tranexamic acid (80 vs 31%; P<0.001). Use of rescue medication within the first 12 hours was administered in 3/26 patients (11%) receiving icatibant compared to 13/29 patients (45%) receiving placebo, and within the first 48 hours in 6/26 (22%) and 15/29 (52%) patients, respectively. Similar results were observed with icatibant compared to tranexamic acid (0/36 [0%] vs 5/38 [13%] and 6/36 [17%] vs 11/38 [29%]; P values not reported). The most common adverse events were recurrent or worsening angioedema.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Injection site reactions, which were recorded separately from the other adverse events, were reported by the majority of patients in each trial, and by more patients treated with icatibant (96 vs 28% and 97 vs 26%). In both trials, the proportions of patients reporting any adverse event were 44 vs 66% and 53 vs 42%. No serious adverse events occurred in FAST-1, while 11 vs 3% of patients reported a serious adverse event in FAST-2 (P values not reported).
Lumry et al.[36] (2011) FAST-3 Icatibant 30 mg SC once vs placebo Patients with severe laryngeal angioedema were treated with OL icatibant.	DB, MC, PC, PRO, RCT Patients ≥18 years of age with a diagnosis of HAE type I or II presenting within six to 12 hours after a mild to severely acute HAE attack	N=93 Single attack trial	Primary: Time to 50% reduction in symptom severity of cutaneous and/or abdominal attacks Secondary: Time to onset of primary symptom relief, time to almost complete symptom relief, time to initial symptom improvement assessment by the patient and investigator, time to onset of symptom relief, time to onset of symptom relief of individual symptoms, rescue medication	Primary: Median time to 50% reduction in symptom severity was significantly shorter with icatibant compared to placebo (2.0 vs 19.8 hours; P<0.001). The reduction in mean VAS score was significantly greater with icatibant compared to placebo from one hour following treatment (P=0.003), and was maintained for eight hours. Secondary: For non-laryngeal attacks, icatibant was associated with a significantly shorter time to onset of primary symptom relief compared to placebo (1.5 vs 18.5 hours; P<0.001). For non-laryngeal attacks, icatibant was associated with a significantly shorter time to almost complete symptom relief compared to placebo (8.0 vs 36.0 hours; P=0.012). For non-laryngeal attacks, icatibant was associated with a significantly shorter time to patient (0.8 vs 3.5 hours; P<0.001) and investigator-assessed (0.8 vs 3.4 hours; P<0.001) initial symptom relief compared to placebo. For non-laryngeal attacks, icatibant was associated with a significantly shorter time to onset of symptom relief for investigator-assessed composite symptom score (1.6 hours vs not reported; P<0.001) compared to placebo. For non-laryngeal attacks, icatibant was associated with a significantly shorter time to onset of symptom relief for individual symptom VAS scores compared to placebo (skin swelling, 3.0 vs 22.3 hours; P<0.001; skin pain, 2.0 vs 8.0 hours; P=0.013; abdominal pain, 1.8 vs 3.5 hours; P=0.007). For non-laryngeal attacks, no patient treated with icatibant required rescue medication compared to 36% of patients treated with placebo. Significance was achieved with icatibant for both use of rescue medications before the onset of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				symptom relief (P<0.001) and at any time point until attack resolution (P<0.001). More patients required rescue medications at any time during the attack and up to five days post-treatment with placebo (40%) compared to icatibant (7%). For laryngeal attacks, the median times to onset of symptom relief were 2.5 and 2.3 hours in patients who received DB and OL treatment with icatibant.
Malbrán et al.[37] (2014) Extension phases of FAST-1 Icatibant 30 mg SC once with repeat doses every six hours PRN (maximum of three injections per attack)	ES, MC, OL, PRO Patients ≥18 years of age with a confirmed diagnosis of HAE types I or II and an attack in the cutaneous, abdominal and/or laryngeal areas severe enough to warrant treatment	N=72 39 months	Primary: Time to onset of primary symptom relief (assessed by VAS) Secondary: Time to almost complete symptom relief, investigators' global assessment, patient-reported time to initial symptom improvement, and adverse events	Primary: The median time to onset of primary symptom relief for cutaneous and/or abdominal attacks ranged between 1.0 and 2.0 hours for attacks one through ten. Secondary: The median time to almost complete symptom relief for cutaneous and/or abdominal attacks ranged between 4.7 to 55.0 hours for attacks one through ten. The investigators' global assessment demonstrated an improvement in symptom severity for both cutaneous and abdominal attacks within four hours regardless of pretreatment attack severity. For laryngeal attacks, the investigator's global assessment showed a rapid improvement in symptom severity within four post-dose and by 24 hours post-icatibant treatment, all laryngeal symptoms were reported as mild or absent. The median time to patient-reported initial symptom improvement for cutaneous and/or abdominal attacks ranged between 0.4 and 0.8 hours for attacks one through ten. The median patient-assessed time to initial symptom improvement for laryngeal attacks ranged from 0.1 to 5.3 hours across all attacks. Adverse events were reported by 81.9% of patients and most events were mild-to-moderate in severity.
Lumry et al.[38] (2015) Extension phases of FAST-3 Icatibant 30 mg SC once with repeat doses	ES, MC, OL, PRO Patients ≥18 years of age with a confirmed diagnosis of type I or type II HAE who were	N=98 Three years	Primary: Time to onset of symptom relief (defined as the earliest of three consecutive time points at which a ≥50% reduction in the patient-reported	Primary: Across the groups of patients with first, second, third, fourth or fifth icatibant-treated HAE attacks, the median time to onset of symptom relief was 1.9 to 2.1 hours. Secondary: The median time to onset of primary symptom relief was 1.5 to 2.0 hours. The median time to almost complete symptom relief was 3.5 to 19.7 hours. The median time to initial symptom improvement was 0.5 to 0.8 hours when assessed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every six hours PRN (maximum of three injections per attack)	experiencing a moderate-to-very-severe cutaneous or abdominal HAE attack or a mild-to-moderate laryngeal HAE attack		composite VAS score was achieved) Secondary: Time to onset of primary symptom relief, time to almost complete symptom relief, time to initial symptom improvement, and adverse effects	by the patient and 0.6 to 0.9 hours when assessed by the investigator. Largely overlapping 95% CI supported the consistency of each of these outcomes across the multiple icatibant-treated attacks. In the repeated-treatment population, ≥1 adverse event was experienced by 39.8%, 35.7%, 36.4%, 21.6%, and 22.6% of patients who had one, two, three, four or five icatibant-treated attacks, respectively.
Riedl et al.[39] (2014) Study 1310 rhC1INH (Ruconest®) 50 IU/kg up to a maximum dose 4,200 of IU/treatment vs placebo	DB, MC, PC, PRO, RCT Patient ≥13 years of age (US or Canada) or ≥18 years of age (other sites) with a confirmed diagnosis of HAE, a current eligible acute HAE attack (peripheral, abdominal, facial, and/or oropharyngeal-laryngeal attack location) with onset within the last five hours, no evidence of regression of	N=75 Single attack trial	Primary: Time to onset of sustained relief for the primary attack location (based on the TEQ) Secondary: Time to minimal symptoms at all affected locations and adverse events	Primary: The time to onset of sustained relief from symptoms at the primary attack location (based on the TEQ) was significantly shorter in patients treated with rhC1INH than in patients treated with placebo (90 vs 152 minutes; P=0.031). Secondary: The time to minimal symptoms at all attack locations (based on the TEQ) was shorter in patients treated with rhC1INH than in patients treated with placebo; however, this difference was not statistically significant (303 vs 483 minutes; P=0.078). Two patients treated with rhC1INH experienced treatment-emergent adverse events of mild severity (procedural headache and fibrin D-dimer increase) that occurred within four hours after dosing. Three patients experienced severe treatment-emergent adverse events (urinary tract infection and abdominal hernia in the rhC1INH group; sinus congestion in the placebo group), which were judged by the investigator not to be related to study medication.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	symptoms, and no history of rabbit allergy			
Li et al.[40] (2015) rhC1INH (Ruconest®) 50 IU/kg IV (up to a maximum dose of 4,200 IU) once, with a second dose PRN one hour later	ES, MC, OL, PRO Patients ≥ 13 years of age (US or Canada) or ≥18 years of age (other sites) with a confirmed diagnosis of HAE, a current acute HAE attack with onset within the last five hours, and no history or rabbit allergy	N=44 Study time frame not documented	Primary: The time to beginning of relief of symptoms at the primary attack location (based on the TEQ) Secondary: Time to minimal symptoms at all affected locations for the first three attacks, proportion of attacks responding to treatment, and adverse events	Primary: The median time to the beginning of relief of symptoms at the primary attack location (based on the TEQ) was 90.0 minutes (95% CI, 33 to 212 minutes) for first attacks, 76.0 minutes (95% CI, 60 to 105 minutes) for second attacks, 134.0 minutes (95% CI, 75 to 150 minutes) for third attacks, 76.5 minutes (95% CI, 58 to 150 minutes) for fourth attacks, 62.5 minutes (95% CI, 48 to 90 minutes) for fifth attacks, and 75.0 minutes (95% CI, 69 to 89 minutes) overall. Secondary: The time to minimal symptoms at all affected locations (based on the TEQ) was 243.0 minutes (95% CI, 76 to 1,440 minutes) for first attacks, 304.0 minutes (95% CI, 150 to 719 minutes) for second attacks, 272.0 minutes (95% CI, 210 to 480 minutes) for third attacks, and 303.0 minutes (95% CI, 211 to 367 minutes) overall. The proportion of attacks responding to treatment with rhC1INH (based on the TEQ) was 82% for first attacks, 92% for second attacks, 86% for third attacks, 78% for fourth attacks, 94% for fifth attacks, and 84% overall. Treatment-emergent adverse events within 72 hours of completion of infusion that were mild or moderate in severity were reported by 27% of patients. This finding was similar to events reported during the RCT phase of the study. Adverse events occurring ≥5% of patients within 72 hours of the completion of infusion were nasopharyngitis, elevated D-dimer concentration, headache, and cough.
Riedl et al.[41] (2013) rhC1INH (Ruconest®) 50U/kg once, with an optional second dose PRN based on clinical	ES, MC, OL, PRO Patients ≥12 years of age with a diagnosis of HAE, without a rabbit allergy, and with an attack <5 hours	N=62 35 months	Primary: Time to beginning of sustained relief of symptoms (defined as the time to the first time point at where overall severity VAS decreased by >20	Primary: The median times to the beginning of symptom relief for the first five attacks were between 37 and 67 minutes. Secondary: The median time to minimal symptoms for the first five attacks were between 120 and 244 minutes. Response rates exceeded 90% and no attack relapses were observed. Few patients took medications that may have interfered with efficacy assessments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
response	from symptom onset		mm compared to baseline for two consecutive VAS recordings for any eligible location) Secondary: Time to minimal symptoms, response rate, relapse rate, development of new attack locations within 24 hours, the use of medication that may have interfered with efficacy assessments, and adverse events	No patient required treatment with any other HAE-specific therapy for the treated attack. The development of a new attack location after treatment occurred for one patient. The most frequently reported adverse events were headache and nasopharyngitis The majority of adverse events were mild to moderate in severity.

Study abbreviations: CI=confidence interval, DB=double blind, ES=extension-study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group PRO=prospective, RCT=randomized controlled trial, XO=cross-over
Miscellaneous abbreviations: C1-INH=C1 esterase inhibitor, HAE=hereditary angioedema, HCP=healthcare professional, IV=intravenous, PRN=as-needed, PU=plasma units, rhC1INH= recombinant human C1 inhibitor, SC=subcutaneous , TEQ=Treatment Effect Questionnaire, VAS=visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Complement Inhibitors for the Treatment of HAE

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Berotralstat hydrochloride	oral capsule	Orladeyo®	$$$$$	N/A
C1 esterase inhibitor, human	intervenous injection, subcutaneous injection	Berinert®, Cinryze®, Haegarda®	$$$$$	N/A
C1 esterase inhibitor, recombinant	intervenous injection	Ruconest®	$$$$$	N/A
Icatibant	subcutaneous injection	Firazyr®*, Sajazir®*	$$$$$	N/A
Lanadelumab-flyo	subcutaneous injection	Takhzyro®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.

X. Conclusions

The complement inhibitors included in this review are approved either for the prophylaxis of HAE attacks or for the treatment of acute HAE attacks. Icatibant is available in a generic formulation. The human C1 esterase inhibitors Cinryze® and Haegarda® are approved for routine prophylaxis against HAE attacks. The kallikrein inhibitors lanadelumab-flyo (Takhzyro®) and berotralstat hydrochloride (Orladeyo®) are also approved for routine prophylaxis against HAE attacks. The human C1 esterase inhibitor (Berinert®), the recombinant C1 esterase inhibitor (Ruconest®), and icatibant (Firazyr®) are all approved for the treatment of acute attacks of HAE.[3-11]

Consensus guidelines recommend that all patients receive on-demand treatment as soon as possible for any acute HAE events, regardless of the location of the swelling or the severity of the attack. Recommended agents for on-demand treatment include C1 esterase inhibitors, icatibant, and ecallantide. Short-term prophylaxis should be considered prior to known patient-specific triggers and for any medical, surgical, or dental procedures. Long-term prophylaxis may be appropriate for some patients (e.g., patients with frequent or severe attacks) to reduce frequency, duration, and severity of attacks. Recommended agents for prophylaxis include attenuated androgens, antifibrinolytic agents, C1 esterase inhibitors, and lanadelumab-flyo. The choice of agent should be based on contraindications, adverse events, risk factors for adverse effects, tolerance, response to intervention, dose required to control attacks, and C1-INH levels. Treatment with berotralstat hydrochloride has not been incorporated into clinical practice guidelines.[12-16]

Numerous clinical trials have evaluated the efficacy and safety of complement inhibitors for the prophylaxis and treatment of HAE events. Several studies have demonstrated similar efficacy among the agents. There have been no head-to-head trials to evaluate the efficacy of the complement inhibitors compared to one another.[17-41] The safety and efficacy of lanadelumab-flyo was studied in a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients 12 years of age and older with type I or II HAE who experienced at least one investigator-confirmed HAE attack per four weeks during the run-in period. The primary endpoint of the mean rate of HAE attacks from day 0 to 182 was lower in the three lanadelumab-flyo treatment groups at 0.48, 0.53, and 0.26, respectively compared to placebo at 1.97 ($P<0.001$ for all comparisons).[24] The safety and efficacy of berotralstat hydrochloride was studied in a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients 12 years of age and older with type I or II HAE who experienced at least two investigator-confirmed HAE attacks within 56 days after the screening visit. The primary endpoint of the rate of monthly HAE attacks during the 24-week treatment period was 1.65 and 1.31 for berotralstat hydrochloride 110 mg and 150 mg, respectively, which was lower than placebo at 2.35 ($P<0.05$ for all comparisons).[9] Berotralstat hydrochloride is the only orally administered complement inhibitor.[17-41]

There is insufficient evidence to support that one complement inhibitor for the treatment of hereditary angioedema is safer or more efficacious than another. The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage, and very specific criteria must be met prior to initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand complement inhibitors within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand complement inhibitor for the treatment of hereditary angioedema is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred agents.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Growth Hormone Agents
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I. Overview

Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid, and carbohydrate compartments. Specifically, body protein content and bone mass increases, total body fat content decreases, and plasma and liver lipid content increases due to the mobilization of free fatty acids from peripheral fat stores. Other physiological effects of GH include stimulation of cartilage growth.[1]

GH therapy has been shown to improve height velocity during childhood in a variety of pediatric conditions where growth is compromised. Early initiation and individualization of GH treatment has the potential to normalize childhood growth in children with idiopathic growth hormone deficiency (GHD).[2] GHD in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A clinical diagnosis is based on auxological features; therefore, a patient's growth patterns are compared to the established norms. The clinical manifestations of GHD will vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients will present with early severe growth failure, delayed bone age, central disposition of body fat, and very low serum concentrations of GH, insulin growth factor 1 (IGF-1), and IGF binding protein-3 (IGFBP-3). GHD in pediatric patients with partial deficiency may be more difficult to diagnose, as these manifestations may not be as obvious. Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated in children with open epiphyses and continued until cessation of linear growth. Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age. Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous injection, are currently the most widely utilized. Pegylated, sustained-release GH, administered by subcutaneous injection, is a newer formulation that is administered once weekly. Due to the variability in individual response to therapy, after initial dosing; the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. Possible explanations of an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH, or the patient has GHD but with concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 centimeters per year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood. The majority of pediatric patients with idiopathic, isolated GHD in their childhood will have normal GH secretion during late adolescence and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies, and/or those with structural defects in the hypothalamic-pituitary region, rarely recover the ability to secrete GH as an adult. Thus, retesting may not be required in these cases.[1]

GHD may also occur in adult patients; however, the role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. A variety of adult studies have highlighted the positive effects of GH on overall body composition, cardiovascular risk profile, bone structure, and psychologic wellbeing. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood-onset or adult-onset.[2]

All of the GH preparations contain somatropin (otherwise known as recombinant human GH), with the exception of lonapegsomatropin-tcgd, which is a pegylated prodrug of somatropin Food and Drug Administration (FDA)-approved in August 2021.[3-11] These various preparations are FDA-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, born small for gestational age, Prader-Willi syndrome, mutations in the short stature homeobox-containing (SHOX) gene, Noonan syndrome, and idiopathic short stature.[3-8,10] The majority of preparations are also indicated for the treatment of GHD in adults.[3-8,10] Serostim® (somatropin) is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults.[9] Most formulations of recombinant human GH

are FDA-approved for use in pediatric patients who have failure in growth due to growth hormone decifiency; however, lonapegsomatropin-tcgd (Skytrofa®) is the only GH approved for use in a specific pediatric population for this indication including those one year and older who weigh ≥11.5 kg.[3-8,10,11] Specific FDA-approved indications for the various GH preparations are outlined in Table 3. All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.

Table 1. Growth Hormone Agents Included in this Review[3-11]

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Lonapegsomatropin-tcgd	subcutaneous injection (cartridge)	Skytrofa®	none
Somatropin	subcutaneous injection	Genotropin® Humatrope® Norditropin® Nutropin® Omnitrope® Saizen® Serostim® Zomacton®	Omnitrope®cc, Zomacton®cc

PDL=Preferred Drug List
[cc]Denotes agent is preferred with clinical criteria in place.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the growth hormone agents are summarized in Table 2.

Table 2. Treatment Guidelines for Growth Hormone Agents

Clinical Guideline	Recommendation(s)
Endocrine Society: **Evaluation and Treatment of Adult Growth Hormone Deficiency (2011)**[12]	<u>Definition of GHD in adults</u> • Patients with childhood-onset GHD who are candidates for GH therapy after adult height is achieved are recommended to be retested for GHD unless they have known mutations, embryopathic lesions causing multiple hormone deficits, or irreversible structural lesions/damage. • In adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies, consideration for evaluation for acquired GHD is recommended. • The use of two tests before making a diagnosis of idiopathic GHD is suggested because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test. The presence of a low IGF-1 also increases the likelihood of this diagnosis. <u>Diagnosis of GHD</u> • The insulin tolerance test and the growth hormone releasing hormone (GHRH)-arginine (ARG) test have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, in those with clearly established, recent (within 10 years) hypothalamic causes of suspected GHD (e.g., irradiation) testing with GHRH-ARG may be misleading. • When GHRH is not available and insulin tolerance test is either contraindicated or not practical in a given patient, it is recommended that the glucagon test be used. • Because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least one month off GH therapy is recommended as sufficient documentation of persistent GHD without additional provocative testing. • A normal IGF-I level does not exclude the diagnosis of GHD, but provocative testing is recommended as mandatory to make the diagnosis of GHD. A low IGF-I

Clinical Guideline	Recommendation(s)
	level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing. • Provocative testing is optional in patients with deficiencies in three or more pituitary axes as GHD is strongly suggested. Consequences of GHD and benefits of treatment with GH • GH therapy of GH-deficient adults offers significant clinical benefits in body composition, exercise capacity, and skeletal integrity. • After documentation of persistent GHD, it is recommended to continue GH therapy after completion of adult height to obtain full skeletal/muscle maturation during the transitional period. • GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness, and aspects of myocardial function, but tends to increase insulin resistance. • GH has not yet been shown to improve mortality, but it is recommended that it does improve the quality of life of most patients. Side effects and risks associated with GH therapy • Treatment is contraindicated in the presence of active malignancy. • It is recommended that GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications. • Monitoring of thyroid and adrenal function during therapy with GH is suggested. Treatment regimens • GH dosing should be individualized rather than weight-based and started with low doses titrated according to clinical response, side effects, and IGF-1 levels. • It is recommended that GH dosing take into consideration gender, estrogen status, and age. • Monitoring patients at one- to two-month intervals during dose titration and semiannually thereafter for adverse effects, IGF-1 levels, and other parameters of GH response is suggested.
American Association of Clinical Endocrinologists and American College of Endocrinology: **Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care (2019)**[13]	• The most common causes of childhood-onset-GHD and adult-onset GHD are isolated idiopathic GHD and hypothalamic-pituitary tumors and/or their treatment regimens, respectively; hence, the possibility of GHD should be considered in these patients. • Several nontumoral causes of adult GHD (e.g., traumatic brain injury, subarachnoid hemorrhage, ischemic stroke, and infections in the central nervous system) have been increasingly described in the past decade, and screening may be considered although the accuracy and reliability of GH-stimulation tests for the diagnosis of adult GHD have not been studied extensively in these populations. • It is recommended that adults with childhood-onset-GHD caused by structural pituitary or brain tumors be followed up closely during transition as these patients tend to have lower bone mineral density, impaired bone microarchitecture, and more adverse body composition abnormalities and cardiovascular risk markers than those with adult-onset GHD. • Resuming recombinant human GH replacement therapy in patients with confirmed persistent GHD during the transition period after achievement of final height is recommended, as most studies have reported long-term improvement in body composition, bone health, quality of life, and lipid metabolism in adulthood. Recommendations for testing for adult GHD • GH-stimulation test/s should only be performed based on the appropriate clinical context of each individual patient with a history suggestive of a reasonable clinical

Clinical Guideline	Recommendation(s)
	suspicion of GHD, and with the intent to initiate recombinant human GH replacement if the diagnosis is confirmed. • The diagnosis of adult GHD can be made without the need for performing GH-stimulation testing in certain patient subtypes, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) and biochemical evidence of multiple pituitary hormone deficiencies (≥3 pituitary hormone deficiencies) together with low-serum IGF-1 levels (<-2.0 standard deviation score), genetic defects affecting the hypothalamic-pituitary axes, and hypothalamic-pituitary structural brain defects. • In patients with ≤2 pituitary hormone deficiencies, low-serum IGF-1 levels (<-2.0 standard deviation score) alone are not sufficient to make a diagnosis of adult GHD; clinicians should perform one GH-stimulation test to confirm the diagnosis. • After longitudinal growth is completed in transition patients with idiopathic isolated GHD, those with low-normal or low serum IGF-1 levels should be retested for GHD with GH-stimulation tests after at least 1 month following discontinuation of recombinant human GH therapy. • After longitudinal growth is completed in transition patients with isolated GHD and the presence of organic hypothalamic-pituitary disease the number of GH-stimulation tests to be undertaken should be guided by the degree of clinical suspicion for GHD. If clinical suspicion is high, one GH-stimulation test is sufficient, but if clinical suspicion is low, then a second GH-stimulation test should be performed. • To continue recombinant human GH replacement in adulthood, retesting for GHD with GH-stimulation test(s) is recommended in most transition patients, especially patients with idiopathic isolated GHD and serum IGF-1 standard deviation score <0, when longitudinal growth is complete, and at least one month after discontinuation of pediatric recombinant human GH therapy. • Patients with idiopathic GHD and serum IGF-1 ≥0 standard deviation score are likely to have a normal GH-stimulation test; hence, retesting and recombinant human GH therapy in these patients after completion of longitudinal growth are not required. • Retesting is not required in transition patients with multiple pituitary hormone deficiencies and low-serum IGF-1 levels patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects, and recombinant human GH therapy may be continued in these patients without interruption. • The risk for development of persistent GHD after radiation therapy is increased with higher radiation doses and longer duration of time since the therapy. Retesting those patients who initially test as GH-sufficient may be performed later in the transition period or in adulthood to rule out delayed GHD. • Traumatic brain injury and subarachnoid hemorrhage are now recognized clinical conditions that may cause GHD, but because GHD may be transient in these patients, GH-stimulation testing should be performed only after at least 12 months following the event. • Random serum GH and IGF-1 levels cannot be used alone to make the diagnosis of adult GHD, and GH-stimulation test(s) should be performed to confirm the diagnosis with the exception of certain subpopulations, such as patients with organic hypothalamic pituitary disease who have multiple pituitary hormone deficiencies and low serum IGF-1 levels, patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects. • GH-stimulation tests should only be performed after all other pituitary hormone deficiencies have been optimally replaced with stable hormone replacement doses. • The insulin tolerance test remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of 5 µg/L. For adults suspected to have

Clinical Guideline	Recommendation(s)
	GHD and if the insulin tolerance test is contraindicated or is not feasible to be performed in these patients, the glucagon-stimulation test and the macimorelin test could be considered as alternative tests. • For transition patients, a feasible and validated GH-stimulation test has been less well studied. In this patient population, the insulin tolerance test may be utilized, but if the test is contraindicated or not feasible to be performed, the glucagon-stimulation test and the macimorelin test can be considered as alternative tests. • Arginine and levodopa testing have not been systematically evaluated and validated, and because these tests have low sensitivity and specificity in adults and transition patients with suspected GHD, we do not recommend utilizing these tests. <u>Recommendations for initiation and monitoring of recombinant human GH replacement</u> • The use of one commercial recombinant human GH product is not suggested over another, as there is no evidence that one recombinant human GH product is more advantageous than another. • It is recommended to use serum IGF-1 as the biomarker for guiding recombinant human GH dose adjustments. • It is recommended to individualize recombinant human GH dosing independent of body weight, starting with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects. • Serum IGF-1 levels should be targeted within the age-adjusted reference range provided by the laboratory utilized. This decision should consider the pretreatment IGF-1 standard deviation score and the circumstances and tolerability of each individual patient. Because some patients may only tolerate lower recombinant human GH doses frequently limited by side effects, whereas others may require higher recombinant human GH doses to achieve desired clinical effects, the goals of treatment should be the clinical response, avoidance of side effects, and targeting serum IGF-1 levels to fall within the age-adjusted reference range. • It is recommended to initiate recombinant human GH therapy using low GH dosages (0.1 to 0.2 mg/day) in GH-deficient patients with concurrent diabetes mellitus, obesity, older age, and previous gestational diabetes mellitus to avoid impairment of glucose metabolism. Higher recombinant human GH starting doses (0.3 to 0.4 mg/day) are advised in nondiabetic young adults <30 years of age and women on oral estrogen therapy. • After starting on recombinant human GH therapy, it is recommended to follow patients at 1- to 2-month intervals initially, increasing the recombinant human GH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. Once maintenance doses are achieved, follow-up can be implemented at approximately 6- to12-month intervals. Shorter follow-up time intervals and smaller dose increments can be implemented especially for the elderly, and those with other comorbidities, such as diabetes mellitus. • When maintenance recombinant human GH doses are achieved, the following parameters may be assessed at approximately 6- to 12-month intervals: serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, body mass index, waist circumference, waist-to-hip ratio, serum-free T4, and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin stimulation test, if clinically indicated. • When restarting recombinant human GH therapy in transition patients, resuming recombinant human GH at 50% of the dose used in childhood may be considered. Serum IGF-1 levels should be monitored to avoid exceeding the upper limit of the normal range. The dose should be modified based on the clinical response, serum IGF-1 levels, side effects, and individual patient considerations.

Clinical Guideline	Recommendation(s)
	• In transition patients, annual measurements of height, weight, body mass index, and waist and hip circumference are recommended, measuring bone mineral density and fasting lipids after discontinuing recombinant human GH therapy as a baseline assessment, and subsequently every 2 to 3 years and every year, respectively. • Adults with GHD have an increased risk of cardiovascular morbidity and mortality and developing osteopenia and osteoporosis. As such, patients should be monitored appropriately. • Interactions of GH with other pituitary hormone axes may affect glucocorticoid and thyroid hormone requirements; hence, these hormones should be monitored closely, especially before initiation of recombinant human GH therapy, as introduction of these hormones or dose increments may be required while on recombinant human GH therapy. When stable new glucocorticoid and thyroid hormone doses are established, less frequent monitoring may be undertaken, unless symptoms develop or radiotherapy is administered. • The optimal duration of recombinant human GH replacement therapy remains unclear. If patients on recombinant human GH replacement experience beneficial effects on quality of life and objective improvements in biochemistry, body composition, and bone mineral density, recombinant human GH treatment can be continued indefinitely. <u>Recommendations during conception and pregnancy</u> • Previous studies support the use of recombinant human GH while seeking fertility, and continuing recombinant human GH during pregnancy does not appear to impact the outcomes of either mother or fetus. However, more data are still needed regarding the safety of recombinant human GH. Routine use of recombinant human GH for conception or continued use during pregnancy in women with GHD cannot be recommended at this present time. <u>Recommendations for safety of GH replacement</u> • Side effects are related mainly to fluid retention effects and are typically seen during initiation and dose escalation of recombinant human GH, and generally respond to dose reductions or cessation of therapy. Lower doses of recombinant human GH are recommended in obese and older patients who are generally more susceptible to the side effects of recombinant human GH replacement. • It is recommended to avoid the use of high recombinant human GH doses to minimize the risk of side effects and aim to maintain target serum IGF-1 levels within the age-adjusted laboratory reference range. • If diabetes mellitus develops during recombinant human GH therapy, or if recombinant human GH therapy is considered in patients with concurrent diabetes mellitus, use of low-dose recombinant human GH therapy, and addition and/or adjustments in antidiabetic medications are suggested. If pre-existing diabetes worsens while on recombinant human GH therapy, it is reasonable to initiate or increase the doses of antidiabetic therapy or discontinue recombinant human GH therapy and optimize treatment of diabetes mellitus first before considering resuming recombinant human GH therapy in these patients. • Treatment with recombinant human GH in patients with a history of active malignancy (other than basal-cell or squamous-cell skin cancers) and active proliferative or severe nonproliferative diabetic retinopathy is contraindicated. • Treatment with recombinant human GH should be conducted with caution in patients with a strong family history of cancer. • For adults with GHD and a history of cancer who have expressed a desire to start recombinant human GH replacement therapy, such therapy may be considered based on each individual circumstance, and low-dose recombinant human GH therapy should only be initiated at least five years after cancer remission is achieved and after discussion with the patient's oncologist.

Clinical Guideline	Recommendation(s)
	• After over 20 years of adult recombinant human GH replacement, there are no data to suggest that recombinant human GH replacement in adults increases the risk of cancer or accelerates recurrences of tumors in the hypothalamic-pituitary region; however, for the purposes of safety surveillance, continued long-term monitoring and standard cancer screening should still be performed.
National Institute for Health and Clinical Excellence: **Human Growth Hormone (Somatropin) for the Treatment of Growth Failure in Children (2010)**[14]	• Somatropin is recommended as a treatment option for children with growth failure associated with growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age of later, short statue homeobox-containing gene (SHOX) deficiency • Treatment with somatropin should be initiated and monitored by a pediatrician with specialist expertise in managing growth hormone disorders after informed discussed about the advantages and disadvantages of the products available. • Treatment with somatropin should be discontinued if growth velocity increase less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than two centimeters total growth in one year, there are insurmountable problems with adherence, or final height is achieved. • In Prader-Willi syndrome evaluation of response to therapy should also consider body composition • The decision to stop treatment should be made in consultation with the patient and/or carers by a pediatrician with specialist expertise in managing growth hormone disorders in children or an adult endocrinologist.
National Kidney Foundation: **Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in Children with Chronic Kidney Disease: 2008 Update (2008)**[15]	• Identification and treatment of existing nutritional deficiencies and metabolic abnormalities should be aggressively pursued in children with chronic kidney disease (CKD) stages two to five and five D, short stature (height standard deviations [SD] <-1.88 or height-for-age <3rd percentile), and potential for linear growth. • Recombinant human growth hormone therapy should be considered in children with CKD stages two to five and five D, short stature (height standard deviation score <-1.88 or height-for-age <3rd percentile) persists beyond three months despite treatment of nutritional deficiencies and metabolic abnormalities.
DYSCERNE: **Management of Noonan Syndrome: A Clinical Guideline (2010)**[16]	• Nearly half of children with Noonan Syndrome (NS) will reach a height within the normal range without growth hormone intervention. • Modest response to growth hormone therapy has been documented by some NS patients will continue to grow into their late teens or early twenties because of late puberty and thereby reach normal range. Final height may also be influenced by parental height. • If height is below 2.5 standard deviations from the mean on standard childhood charts, growth hormone therapy may be considered without evaluation of the growth hormone axis. If IGF-1 levels are low, testing of the GH axis should be considered to show growth hormone deficiency. • There is no data to support the claim that existing hypertrophic cardiomyopathy (HCM) or malignancy are relative contraindications to growth hormone therapy. There is no evidence of an increased risk of HCM or malignancy developing in people with HS undertaking growth hormone therapy.
Noonan Syndrome Support Group: **Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines**	• Children should be weighed and measured regularly by the primary care provider and plotted on appropriate growth charts. (Three times yearly for the first three years of life, and yearly thereafter.) • Children with evidence of growth failure (growth deceleration, height <-2 standard deviations, or height inappropriate for genetic background) that cannot be explained by a comorbidity should be monitored more often, have nutrition optimized, have baseline labs obtained and/or referred to a pediatric

Clinical Guideline	Recommendation(s)
(2010)[17]	endocrinologist. • Therapeutic interventions as indicated (growth hormones for growth failure, thyroid hormone replacement for hypothyroidism, estrogen or testosterone for pubertal delay).
Growth Hormone Research Society: **Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome (2013)[18]**	• After genetic confirmation of Prader-Willi syndrome (PWS), GH therapy should be considered and, if initiated, continued for as long as demonstrated benefits outweigh the risks. • GH stimulation testing should not be required as part of the decision-making process in infants and children with PWS. • Adults with PWS should have an evaluation of the GH/IGF axis prior to GH treatment. • Prior to initiation of GH treatment, patients with PWS should have a genetically confirmed diagnosis and expert multidisciplinary evaluation. • Exclusion criteria for starting GH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis. • Scoliosis is not a contraindication to GH treatment in patients with PWS. • Infants and children with PWS should start with a daily dose of 0.5 mg/m^2/day subcutaneously with subsequent adjustments toward 1.0 mg/m^2/day every three to six months according to clinical response and guided by maintenance of physiologic levels of IGF-I. • Adults with PWS should receive a starting dose of 0.1 to 0.2 mg/day based on age, presence of edema, prior GH treatment, sensitivity and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age, and sex appropriate IGF-I levels in the zero to two standard deviation range. • IGF-I levels in patients with PWS on GH treatment should be maintained within the upper part of normal range (one to two standard deviations) for healthy, age-matched normal individuals. • Clinical outcome priorities should vary depending on the age and on the presence of physical, mental and social disability. • Monitoring GH treatment in patients with PWS should address specific benefits and risks of treatment in this population and the potential impact of other hormonal deficiencies. • Patients with PWS receiving GH treatment must be followed carefully for potential adverse effects during GH treatment. • Treatment with GH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with PWS. • Cognitive impairment should not be a barrier to treatment with GH for patients with PWS.
Expert Meeting of the Comprehensive Care of Patients with Prader-Willi Syndrome: **Recommendations for the Diagnosis and Management of Prader-Willi Syndrome (2008)[19]**	• GH therapy should be started early in childhood, taking into account cautions and relative contraindications. • Appropriate monitoring of GH replacement is essential. • Before starting GH therapy, there should be genetic confirmation of Prader-Willi syndrome, nutritional evaluation and evaluation of IGF-1 status and, if possible, GH status. Additionally, an oral glucose tolerance test, scoliosis evaluation, sleep and breathing evaluation, and evaluation of hypothyroidism are recommended. • During GH treatment, regular clinical assessment of height, weight, body mass index, body composition, pubertal status, scoliosis, IGF-1, and side effects are recommended every three to six months. Regular bone age and monitoring for hypothyroidism are also recommended. • Cessation of GH treatment should be considered if there is uncontrolled progression of obesity, continued worsening of glycemic control, continued worsening of sleep-disordered breathing or attainment of final height.
Turner Syndrome Study Group:	• Provocative GH testing should only be performed in patients with abnormal growth relative to expected for Turner syndrome on a Turner syndrome specific

Clinical Guideline	Recommendation(s)
Care of Girls and Women with Turner Syndrome (2007)[20]	growth curve. • Treatment with GH should be considered as soon as growth failure has been demonstrated. • GH doses can be changed based on growth response and IGF-1 levels. • Therapy may be continued until final height has been attained or little growth potential remains. • For girls below approximately nine years of age, therapy is usually started with GH alone. In older girls, or those with extreme short stature, consideration can be given to using higher doses of GH and adding a nonaromatizable anabolic steroid. • Therapy should be directed by a pediatric endocrinologist and the patient should be monitored every three to six months.
Growth Hormone Research Society/Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology: **Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature (2008)[21]**	• Other causes of short stature (e.g., GHD) must be ruled out in order to make a diagnosis of ISS. • The height below which GH treatment could be considered is -2 to 3- standard deviation score. • Age should be taken into consideration when initiating GH therapy. • There are no biochemical criteria for initiating GH treatment in ISS. • Predicted adult height can be used with other criteria (family pubertal history and midparental target height) to decide to treat with GH therapy. • A successful first year response can be defined as a change in height standard deviation score more than 0.3 to 0.5, a first-year height velocity increment of more than 3 cm/year, or a height velocity of standard deviation score more than +1. • Serial IGF-1 measurements during GH therapy are useful to assess efficacy, safety, and compliance. • Children treated with GH should be monitored for height, weight, pubertal development, and adverse effects at 3- to 6-month intervals. Regular monitoring for scoliosis, tonsillar hypertrophy, papilledema, and slipped capital femoral epiphysis should be performed as part of the regular physical exam during follow-up visits. We recommend that after 1 year, the response to therapy be assessed by calculating height velocity standard deviation score as well as the change in height standard deviation score. • Therapy can be stopped when near adult height is achieved (height velocity of <2 cm/year and/or bone age >16 years in boys and >14 years in girls) or when height is in the normal adult range (above -2 standard deviation score).
Pediatric Endocrine Society: **Guidelines for Growth Hormone and Insulin-Like Growth Factor-1 Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-1 Deficiency (2016)[22]**	<u>Efficacy of GH Treatment for GHD</u> • The use of GH is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD. <u>Consideration and Diagnosis of GHD</u> • Establishing a diagnosis of GHD without GH provocative testing in patients possessing auxological criteria, hypothalamic-pituitary defect, and deficiency of at least one additional pituitary hormone. • GHD due to congenital hypopituitarism should be diagnosed without formal GH provocative testing in a newborn with hypoglycemia who does no attain a serum GH concentration above 5 µg/L and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad. • GH provocative testing is not recommended as the sole diagnostic criterion of GHD. • Sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with adult height prognosis within -2 standard deviation of the reference population is recommended in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty. <u>Dosing of GH Treatment for Patients with GHD</u>

Clinical Guideline	Recommendation(s)
	• It is recommended that weight-based or body surface area-based GH dosing be used in children with GHD. • An initial dose of 0.16 to 0.24 mg/kg/week is recommended with individualization of subsequent dosing. • Serum IGF- levels can be used to monitor adherence. It is recommended that GH dose be lowered if serum IGF-1 levels rise above the laboratory-defined normal range for the age of pubertal stage of the patient. • It is not recommended to increase the GH dose to 0.7 mg/kg/week in every child with GHD during puberty. • GH treatment at pediatric doses should not be continued beyond attainment of growth velocity below 2 to 2.5 cm per year. <u>Safety Issues of GH Treatment for Patients with GHD</u> • It is recommended to monitor for the potential development of intracranial hypertension, clipped capital femoral epiphysis, and scoliosis progression. • Re-assessment of adrenal and thyroid axes is recommended after initiation of GH therapy in patients whose cause of GHD is associated with possible pituitary hormone deficiencies. • For children with acquired GHD due to effects of the primary malignancy, it is recommended to discuss the risks including the potential effect of GH treatment on the timing of second neoplasm occurrence. A standard waiting period of 12 month is appropriate for GH initiation after completion of tumor therapy with no evidence of ongoing tumor. • It is recommended to inform prospective recipients of GH therapy about the uncertainty regarding long-term safety. <u>Transitional Care after Childhood GH Treatment</u> • It is recommended that patients with multiple (≥3) pituitary hormone deficiencies or GHD with documented causal genetic mutation or specific pituitary/hypothalamic structural defect be diagnosed with persistent GHD. • Re-evaluation of the somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD (IGHD), IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation. • It is recommended to re-evaluate the somatotropic axis if clinically indicated by measuring serum IGF-1 concentration. GH provocative testing can be used to evaluate the function of the somatotropic axis in the transition period if indicated by low IGF-1 level. <u>GH Treatment of Patients with ISS</u> • It is not recommended to routinely use GH in every child with height standard deviation score ≤ -2.25. • Initiation of GH at a dose of 0.24 mg/kg/week up to 0.47 mg/kg/week is suggested. <u>IGF-1 Treatment of Patients with Insulin-like Growth Factor deficiency (PIGFD)</u> • It is recommended to use IGF-1 therapy to increase height in patients with severe PIGFD. • PIGFD diagnosis is based on a combination of four factors including auxological parameters and low IGF-1 concentration, exclusion of secondary causes of IGF-1 deficiency, low levels of GH-binding protein suggesting Laron syndrome/GHIS, and IGF-1 generation test and mutation analyses. • A trial of GH therapy is recommended before initiating IGF-1 for patients with unexplained IGF-1 deficiency.
Growth Hormone	• The goal of treatment of children with GHD is to replace the deficient GH for

Clinical Guideline	Recommendation(s)
Research Society: **Diagnosis, Genetics, and Therapy of Short Stature in Children (2019)**[23]	growth, metabolism, and well-being. Recombinant human GH starting doses • The dose of recombinant human GH should be individualized according to GH responsiveness aiming for the lowest effective dose (i.e., the lowest dose at which there is an appropriate response in height velocity). This needs to be in harmony with local guidelines using doses that are within the indications of the various products and not limited by individual product labeling. • Patients with more severe GHD, as evidenced by lower peak GH levels, lower IGF-1 levels, and clinical features (such as the severity of the growth deficit, bone age delay, presence of additional pituitary deficiencies, anatomical abnormalities on brain magnetic resonance imaging, or genetic defects associated with GHD), should be initially treated with lower doses of recombinant human GH. • For other approved, non-GHD indications, the doses prescribed may need to be higher. It is recommended to start recombinant human GH at the approved dose ranges, possibly using prediction models to aid in dose optimization. • In certain conditions, such as with older small for gestational age patients and in the late diagnosis of Turner syndrome, it is recommended that recombinant GH be started at a dose that is at the higher end of the approved range. In infants and adolescents, patients with obesity and those with Prader-Willi syndrome, recombinant human GH dosing may be based on body surface area rather than weight. Recombinant human GH dose adjustments • The principal parameter to adjust recombinant human GH should be the growth response. • The appropriateness of the recombinant human GH dose should be assessed based on height velocity and change in height standard deviation score every six to twelve months. • The use of IGF-1 serum levels may provide additional information about treatment efficacy, adherence, and, theoretically, safety. • When using IGF-1 levels to adjust dose, the “ideal” level of IGF-1 should, in general, be close to 0 standard deviation score in GHD, but individual adjustments are typically necessary based on auxological measurements. • Once catch-up growth is achieved in patients with GHD, consideration can be given to reducing the recombinant human GH dose with close monitoring for continued normal height velocity. • In non-GHD conditions, such as ISS, IGF-1 levels of approximately +1 standard deviation score or higher are usual, but the target should be adjusted on an individual basis based on auxological measurements. • In certain conditions characterized by partial IGF-1 insensitivity (e.g., Silver-Russell syndrome/small for gestational age, Prader-Willi syndrome, and IGF-1 receptor defects) and Turner syndrome, IGF-1 levels above +2 standard deviation scores may be needed for effective growth. • Low levels of IGF-1 may indicate poor adherence, inadequate storage, or the presence of another condition affecting GH response. • High IGF-1 levels may reflect some degree of IGF-1 insensitivity, especially if associated with poor growth response. Definition and management of suboptimal response to recombinant human GH • An inadequate response after initiation of recombinant human GH therapy in patients with GHD is often defined by one or more of the following criteria: change in height velocity less than cm/year, height velocity standard deviation score <0, or change in height standard deviation score <0.3/year during the first six to twelve months of therapy, but there is considerable variation in response

Clinical Guideline	Recommendation(s)
	according to age and pubertal maturation. • Clinicians should use age, sex, and etiology-specific (including for GHD) response charts to assess individual growth responses after starting recombinant human GH therapy. • For genetic syndromes, standard growth charts should not be used for reference, and disease-specific growth charts should be utilized when available. • When a suboptimal growth response for pubertal status is noted, a review of adherence and injection techniques is indicated. • IGF-1 levels can be used as a measure of adherence and help identify GH or IGF-1 resistance conditions (e.g., onset of scoliosis and chronic illnesses, hypothyroidism, inadequate nutrition, medications that impair growth, challenges in the psychosocial environment, skeletal dysplasia, other genetic conditions). • If no GH or IGF-1 resistance conditions are present, and IGF-1 levels are below the target range, the recombinant GH dose can be increased to determine whether height velocity and the IGF-1 level increases. Recombinant human GH should be discontinued if suboptimal response persists.
European Society for Paediatric Nephrology: **Clinical Practice Recommendations for Growth Hormone Treatment in Children with Chronic Kidney Disease (2019)**[24]	<u>Recommendations for assessing the indications and contraindications for GH treatment</u> • Pros and cons of GH treatment should be discussed with individual patients and their families before GH treatment is initiated. Such discussion is of particular importance for immobilized patients, and those with syndromic kidney diseases. • Children with stage 3 to 5 chronic kidney disease or on dialysis aged above six months are candidates for GH therapy if they have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, once other potentially treatable risk factors for growth failure have been adequately addressed and provided the child has growth potential. • GH therapy should be considered for children with stage 3 to 5 chronic kidney disease or on dialysis aged above six months who present with a height between the third and tenth percentile but persistent low height velocity (below the twenty-fifth percentile) once other potentially treatable risk factors for growth failure have been adequately addressed. • In children who have received a kidney transplant and have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, it is recommended to initiate GH therapy one year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option. • In children with chronic kidney disease due to nephropathic cystinosis who have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, GH therapy should be considered at all stages of CKD. • GH therapy should not be started in: o Patients with closed epiphyses o Patients with known hypersensitivity to the active substance or to any of the excipients o Cases of unwillingness of the patient or their family o Patients with severe secondary hyperparathyroidism o Patients with proliferative or severe non-proliferative diabetic retinopathy o Patients during the first year after renal transplantation o Patients with acute critical illness o Patients with active malignancy <u>Recommendations for GH treatment and monitoring</u> • GH should be given at a dose of 0.045 to 0.05 mg/kg body weight per day by subcutaneous injections in the evening. • Parents and physicians should encourage children from about eight to ten years of

Clinical Guideline	Recommendation(s)
	age to do the GH injections on their own if adequate training and adherence is ensured. • Both GH reference and GH biosimilar products are recommended for use in short children with chronic kidney disease. • Clinic visits every three to six months or more frequently are suggested for young patients and those with advanced chronic kidney disease to monitor stature, height velocity, pubertal development, skeletal maturation on wrist radiography, renal function, thyroid hormone, serum glucose, calcium, phosphate, bicarbonate, and parathyroid hormone levels. • If height velocity in the first year of GH treatment is less than two cm per year over baseline, it is recommended to conduct assessments of patient adherence to GH therapy, including measurement of serum IGF-1 levels, weight-adjusted GH dosage, and nutritional and metabolic factors before initiation of GH therapy. • Discontinuation of GH is recommended: o When epiphyseal closure is demonstrated o At the time of renal transplantation o In patients with persistent severe secondary hyperparathyroidism (GH may be reinitiated when levels return to the desired parathyroid hormone target range) o With occurrence of intracranial hypertension o In patients with slipped capital femoral epiphysis o If the patient does not adequately respond to GH treatment despite optimal nutritional and metabolic control o In patients with accelerated bone maturation o In cases of an unexplained decrease in estimated glomerular filtration rate • Cessation of GH treatment should be considered: o When the patient reaches his or her genetic target height percentile (GH may be reinstituted if catch-down growth occurs) o When the patient reaches his or her genetic target height
International Turner Syndrome Consensus Group: **Clinical Practice Guidelines for the Care of Girls and Women with Turner Syndrome (2016)**[25]	Growth and Puberty • Initiate GH treatment early (around four to six years of age, and preferably before twelve to thirteen years of age) in the following circumstances: the child already has evidence of growth failure (e.g., below the 50th percentile height velocity observed over six months in the absence of other treatable causes of poor growth), the child is already short or has a strong likelihood of short stature (e.g., short parents and short predicted adult height or already pubertal at the time of diagnosis). • It is recommended to use a GH dose of 45 to 50 µg/kg/day or 1.3 to 1.5 mg/m^2/day (4.0 to 4.5 /m^2/day) in most instances, increasing to 68 µg/kg/day (2.0 mg/m^2/day) if adult height potential is substantially compromised. • Monitor growth-promoting treatment by measurement of height at least every four to six months during the first year of treatment and at least every six months thereafter. • Monitor the safety of growth-promoting therapy by measurement of IGF-1 at least annually. • For Turner Syndrome patients treated with GH, the measured IGF-1 should ideally be no greater than 2 standard deviation scores above the mean for age. If an IGF-1 value is measured above +3 standard deviation scores, a GH dose decrease is warranted. For an IGF-1 value between +2 SDS and +3 SDS, clinical judgment should guide further GH dose selection. • Concomitant treatment with oxandrolone is suggested from the age of ten years or older at 0.03 mg/kg/day and maintained below 0.05 mg/kg/day, if the diagnosis of Turner Syndrome (and therefore GH treatment initiation) is delayed, and/or adult height outcome is likely to be unsatisfactory with the standard GH dose alone. • Routine addition of very-low-dose estrogen supplementation in the prepubertal

Clinical Guideline	Recommendation(s)
	years to further promote growth is not recommended. • Estrogen replacement should start between 11 and 12 years of age increasing to adult dosing over two to three years. • Low-dose estradiol is the preferred estrogen and should be administered by a systemic route (the transdermal route is preferred). • It is recommended to add progesterone once breakthrough bleeding occurs, or after two years of estrogen treatment.

GH=growth hormone, GHD=growth hormone deficiency, IGF-1=insulin-like growth factor 1, ISS=idiopathic short stature, PIGFD=primary IGF-1 deficiency

III. Indications

The Food and Drug Administration (FDA)-approved indications for the growth hormone agents are noted in Table 3.

Table 3. FDA-Approved Indications for Growth Hormone Agents[3-11]

Indication	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
Pediatric Indications									
Growth failure associated with chronic renal insufficiency before renal transplant					✔ §				
Growth failure associated with Noonan syndrome				✔					
Growth failure associated with Prader-Willi syndrome		✔		✔		✔			
Growth failure associated with short-stature homeobox-containing gene deficiency			✔						✔
Growth failure associated with Turner syndrome		✔	✔	✔	✔	✔			✔
Growth failure in children born small for gestational age		✔ *	✔ †	✔ †		✔ *			✔ †
Growth hormone deficiency	✔ ¶	✔	✔	✔	✔	✔	✔		✔
Idiopathic short stature‡		✔	✔	✔	✔	✔			✔
Adult Indications									
Growth hormone deficiency‖		✔	✔	✔	✔	✔	✔		✔
Human immunodeficiency virus-associated wasting or cachexia								✔	
Treatment of short bowel syndrome in patients receiving specialized nutritional support									

*For patients that fail to manifest catch-up growth by age two years.
†For patients that fail to manifest catch-up growth by age two to four years.
‡Defined by height standard deviation score ≤-2.25 and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.
§Nutropin® should be used in conjunction with optimal management of CKD.
‖For patients who meet either adult-onset criteria (patients who have GH deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma) or childhood-onset criteria (patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes).
¶Skytrofa® is indicated for GH deficiency in pediatric patients who are one year of age and older who weigh ≥11.5 kg.

IV. Pharmacokinetics

The pharmacokinetic parameters of the growth hormone agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Growth Hormone Agents for Subcutaneous Administration[3-11]

Generic (Brand) Name(s)	Bioavailability (%)	Time to Peak Concentration (hours)	Half-Life (hours)
Lonapegsomatropin-tcgd (Skytrofa®)	N/A	25 (prodrug) 12 (active drug)	30.7 (prodrug) 25 (active drug)
Somatropin (Genotropin®)*	80	5.9	3
Somatropin (Humatrope®)	75	N/A	3.8
Somatropin (Norditropin®)*	N/A	4 to 5	7 to 10
Somatropin (Nutropin®)	81	N/A	2.1
Somatropin (Omnitrope®)	N/A	4.0	2.5 to 2.8
Somatropin (Saizen®)	70 to 90	N/A	2
Somatropin (Serostim®)	70 to 90	N/A	4.0
Somatropin (Zomacton®)	70	4.5	2.3

N/A=not available
*Data included is specifically for adult patients with GHD

V. Drug Interactions

Significant drug interactions with the growth hormone agents are listed in Table 5.

Table 5. Significant Drug Interactions with Growth Hormone Agents[3-11]

Generic Name(s)	Interaction	Mechanism
Somatropin*	11 β-Hydroxysteroid Dehydrogenase Type 1	11-β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1) is required for the conversion of cortisone to active metabolite, cortisol. GH inhibits 11βHSD-1. GH treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. Previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. Patients treated with glucocorticoids replacement for previously diagnosed hypoadrenalism may require an increase in maintenance of stress doses.
Somatropin*	Glucocorticoids	Glucocorticoids may attenuate the growth-promoting effects of somatropin in children. Glucocorticoid replacement therapy should be adjusted in children with GH and glucocorticoid deficiency to avoid hypoadrenalism and an inhibitory effect on growth. The use of somatropin in patients with CKD requiring glucocorticoids therapy has not been evaluated. If glucocorticoid replacement is required for CKD, the dose should be adjusted to avoid an inhibitory effect on growth.

Generic Name(s)	Interaction	Mechanism
Somatropin*	Oral estrogen	Oral estrogens may reduce IGF-1 response to somatropin treatment. Greater doses of somatropin may be required in girls and women receiving oral estrogen contraceptives.
Somatropin*	Insulin and/or oral/injectable hypoglycemic agents	The dose of insulin and/or oral/injectable hypoglycemic agents may require adjustment when somatropin therapy is initiated.

CKD=chronic kidney disease, GH=growth hormone, IGF-1=insulin-like growth factor-1
*Given that lonapegsomatropin-tcgd is a prodrug of somatropin, significant drug interactions for somatropin also apply to lonapegsomatropin-tcgd.

VI. Adverse Drug Events

The most common adverse drug events reported with the growth hormones are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with Growth Hormone Agents[3-11]

Adverse Event(s)	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
Body as a whole—general disorders									
Edema, dependent	-	-	-	-	-	-	5	-	6 to 9
Edema, facial	-	-	-	-	-	-	-	-	-
Edema, leg	-	-	-	15	-	-	-	-	-
Edema, generalized	-	✔	-	25	41* <1†	✔ †	5	1 to 6	-
Edema, periorbital	-	-	-	-	-	-	-	1 to <5	-
Edema, peripheral	-	0 to 11*	-	42	-	0 to 11*	15	11 to 26	-
Fatigue	-	2 to 6*	-	-	-	2 to 6*	-	4 to 5	-
Malaise	-	-	-	-	-	-	-	-	-
Pyrexia	15	✔ †	-	-	-	✔ †	-	-	-
Stiffness, extremities	-	0 to 8* ✔ †	-	-	-	0 to 8*	-	-	-
Swelling, peripheral	-	0 to 18*	-	-	-	0 to 18*	-	-	-
Cardiac									
Chest pain	-	-	-	-	-	-	5	-	-
Cardiovascular disorders	-	✔	-	-	-	-	-	-	-
Dermatologic Disorders									
Increase in size/number of cutaneous nevi	-	✔ †	-	✔	-	✔ †	-	-	✔
Moniliasis	-	-	-	-	-	-	-	-	-
Endocrine Disorders									
Decrease in serum T4 (thyroxine) levels	-	-	-	✔	-	-	-	-	-
Diabetes mellitus (new onset, type 2)	-	<1*	-	5	<1†	<1*	-	-	✔
Elevated HbA1c	-	-	-	-	-	14‡ 9§ †	-	-	-
Glucose tolerance abnormal	-	-	-	6	-	-	-	-	-

Adverse Event(s)	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
Gynecomastia	-	✔ †	5	✔	<1†	✔ †	✔ †	4 to 6	✔
Hyperglycemia	-	✔ †	-	-	-	✔ †	-	1 to <5	-
Hypothyroidism	-	✔ †	-	✔	-	16§†	5	-	-
Gastrointestinal Disorders									
Abdominal pain	6	-	-	-	-	-	-	-	-
Diarrhea	6	-	-	-	-	-	-	-	-
Dry mouth	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	-	-	-	-	-	-
Gastritis	-	-	-	-	-	-	-	-	6
Gastroenteritis	-	✔ †	-	8	-	✔ †	-	-	-
Hemorrhoids	-	-	-	-	-	-	-	-	-
Nausea	11‖	-	-	-	-	-	-	5 to 9	-
Pancreatitis	-	✔	-	✔	-	✔	-	-	✔
Tenesmus	-	-	-	-	-	-	-	-	-
Vomiting	11‖	-	-	-	-	-	-	-	-
Hematologic Disorders									
Eosinophilia	-	-	-	-	-	12‡ 11§, †	-	-	-
Hematoma	-	-	-	-	-	9†	-	-	-
Hemorrhage	7	-	-	-	-	-	-	-	-
Leukemia (in children with GHD)	-	✔ †	-	✔ †	-	✔ †	✔ †	-	-
Neoplasm	-	-	-	-	<1†	-	-	-	✔
Hepatic									
Increased alanine aminotransferase	-	-	-	-	-	-	-	-	6
Increased aspartate aminotransferase	-	-	-	-	-	-	-	-	6 to 13
Increase in alkaline phosphatase level	19.2	-	-	✔	-	-	-	-	-
Increase in phosphate level	44.2	-	-	-	-	-	-	-	-
Musculoskeletal Disorders									
Abnormal bone of other growth	-	-	-	-	<1†	-	-	-	-
Arthralgia	6¶	3 to 17* ✔ †	11	19	27* <1†	3 to 17* ✔ †	23	25 to 36	-
Arthrosis	-	-	11	-	-	-	-	8 to 11	-

Adverse Event(s)	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
Asthenia	-	-	-	-	-	-	-	-	3 to 6
Back pain	-	3 to 5*	-	-	-	3 to 5*	-	-	-
Carpal tunnel syndrome	-	2*	-	-	<1†	-	5	1 to <5	-
Fracture	-	✔ †	-	-	<1†	✔ †	-	-	-
Legg-Calvé-Perthes disease	-	✔ †	-	✔	-	-	-	-	-
Myalgia	-	2 to 7*	24	15	-	2 to 7* ✔ †	8	18 to 30	6
Pain, extremities	-	2 to 15*	3	-	-	2 to 15* 5§†	-	-	-
Scoliosis	-	<1†	19	-	<1†	✔ †	-	-	-
Skeletal pain	-	-	-	11		-	5	-	6 to 9
Slipped capital femoral epiphysis	-	✔ †	-	✔	<1†	-	-	-	-
Nervous System Disorders									
Central nervous system tumor	-	-	-	-	<1†	-	-	-	-
Headache	-	0 to 10* ✔ †	-	9	-	0 to 10* 7§†	18	-	9 to 11
Hypoesthesia	-	✔ *	-	-	-	-	7	2 to 5	6
Intracranial hypertension	-	-	-	<1†	-	✔ †	-	-	-
Paresthesia	-	0 to 10*	-	11	-	0 to 10*	7	7	-
Psychiatric									
Depression	-	-	-	-	-	-	5	-	-
Insomnia	-	-	-	-	-	-	5	-	-
Respiratory System Disorders									
Bronchitis	-	-	-	9	-	-	-	-	-
Increased cough	11	-	-	-	-	-	-	-	6
Laryngitis	-	-	-	6	-	-	-	-	-
Nasopharyngitis	-	✔ †	-	-	-	✔ †	-	-	-
Pharyngitis	-		-	-	-		-	-	3 to 14
Upper respiratory infection	-	13 to 16*	-	-	-	13 to 16*	-	-	-

Adverse Event(s)	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
		✔†				✔†			
Respiratory disorder/illness	-	<1†	-	-	-	✔†	-	-	3 to 6
Rhinitis	-	-	-	-	-	-	-	-	6
Tonsillitis	-	✔†	-	-	-	✔†	-	-	
Other									
Acute critical illness	-	✔	-	-	-	-	-	-	-
Aggressiveness	-	✔†	-	-	-	✔†	-	-	-
Alopecia	-	✔†	-	-	-	✔†	-	-	-
Altered mood	-	✔†	-	-	-	✔†	-	-	-
Central precocious puberty	-	<1†	-	-	-	✔†	-	-	-
Diabetic retinopathy	-	✔	-	-	-	-	-	-	-
Ear disorders	-	-	-	-	18†	-	-	-	-
Hematuria	-	✔†	-	-	-	-	-	-	-
Hyperlipidemia	-	-	8	-	-	-	-	-	-
Hypertension	-	-	3	8	-	-	-	-	-
Hypertriglyceridemia	-	-	-	-	-	5§†	-	1 to <5	-
Hypersensitivity	-	-	-	✔	-	✔	✔	-	✔
Increased appetite	-	✔†	-	-	-	✔†	-	-	-
Increased sweating	-	-	-	8	-	-	-	-	-
Infection	-	-	-	13	-	-	-	-	-
Infection bacterial	-	-	-	-	-	-	-	-	-
Infection viral	15	-	-	-	-	-	-	-	-
Influenza/flu-like symptoms	-	✔†	-	8	-	✔†	-	-	16 to 23
Injection site reactions	-	✔†	-	-	<1†	✔†	-	-	-
Jaw prominence	-	<1†	-	-	-	✔†	-	-	-
Lipoatrophy	-	✔†	-	-	-	-	-	-	-
New onset or recurring tumor (benign)	-	-	-	-	<1†	-	-	-	-
Otitis media	-	-	16	-	43†	-	-	-	-
Other Non-Classifiable Disorders	-	-		8	-	-	-	-	-

Adverse Event(s)	Lonapegsomatropin-tcgd (Skytrofa®)	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)[8]	Somatropin (Serostim®)	Somatropin (Zomacton®)
Urinary tract infection	-	<1†	-	-	-	✔ †	-	-	-

* Adult patients
† Pediatric patients
‡Omnitrope® Cartridge only
§Omnitrope® for injection only
‖Includes nausea and vomiting
¶Includes arthralgia and reactive arthritis
✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the growth hormone agents are listed in Table 7.

Table 7. Usual Dosing Regimens for the Growth Hormone Agents[3-11]

Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Lonapegsomatropin-tcgd (Skytrofa®)	Not FDA-approved for use in adults	Treatment of GHD in treatment naïve patients: Cartridge, powder for reconstitution, auto-injector: 0.24 mg/kg SC once weekly, individualize and titrate dosing based on response When changing from daily somatropin therapy to once-weekly lonapegsomatropin-tcgd, wait at least eight hours between the final dose of daily somatropin and the first dose of once-weekly lonapegsomatropin-tcgd	Cartridge, powder for reconstitution: 3 mg 3.6 mg 4.3 mg 5.2 mg 6.3 mg 7.6 mg 9.1 mg 11 mg 13.3 mg
Somatropin (Genotropin®)	Treatment of GHD in adults: Cartridge, powder for reconstitution: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase every one to two months by increments of 0.1 to 0.2 mg per day based on response and serum IGF-1 concentrations; initial (weight-based), 0.04 mg/kg/week SC divided into six or seven doses, increase at four to eight week intervals according to response, adverse effects, and serum IGF-1 concentration; maximum, 0.08 mg/kg/week	Treatment of GHD in pediatrics: Cartridge, powder for reconstitution: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Treatment of ISS: Cartridge, powder for reconstitution: up to 0.47 mg/kg/week SC divided into six or seven doses Treatment of Prader-Willi Syndrome: Cartridge, powder for reconstitution; 0.24 mg/kg/week SC divided into six or seven doses Treatment of SGA: Cartridge, powder for reconstitution; up to 0.48 mg/kg/week SC divided into six or seven doses* Treatment of Turner Syndrome: Cartridge, powder for reconstitution; 0.33 mg/kg/week SC divided into six or seven doses	Cartridge, powder for reconstitution: 5 mg 12 mg Cartridge MiniQuick®, powder for reconstitution (preservative-free): 0.2 mg 0.4 mg 0.6 mg 0.8 mg 1.0 mg 1.2 mg 1.4 mg 1.6 mg 1.8 mg 2.0 mg

Somatropin (Humatrope®)	Treatment of GHD in adults: Cartridge, powder for reconstitution, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase gradually every one to two months by 0.1 to 0.2 mg/day based on response and serum IGF-1 concentrations; initial (weight-based), 0.006 mg/kg SC daily, increase according to response, adverse effects, and serum IGF-1 concentration; maximum 0.0125 mg/kg/day	Treatment of GHD in pediatrics: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.026 to 0.043 mg/kg SC daily Treatment of ISS: Cartridge, powder for reconstitution, vial, powder for reconstitution: up to 0.053 mg/kg SC daily or 0.37 mg/kg/week Treatment of SHOX deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.050 mg/kg SC daily or 0.35 mg/kg/week Treatment of SGA: Cartridge, powder for reconstitution, vial, powder for reconstitution: up to 0.067 mg/kg SC daily or 0.47 mg/kg/week† Treatment of Turner Syndrome: Cartridge, powder for reconstitution, vial, powder for reconstitution: up to 0.054 mg/kg SC daily or 0.375 mg/kg/week	Cartridge, powder for reconstitution: 6 mg 12 mg 24 mg Vial, powder for reconstitution: 5 mg/vial
Somatropin (Norditropin®)	Treatment of GHD in adults: Prefilled pen: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase every one to two months in increments of 0.1 mg to 0.2 mg/day based on response and serum IGF-1 concentrations, initial (weight-based), 0.004 mg/kg SC daily, increase according to response, adverse effects, and serum IGF-1 concentration; maximum: 0.016 mg/kg daily	Treatment of GHD in pediatrics: Prefilled pen: 0.17 to 0.24 mg/kg/week SC divided into six or seven doses Treatment of ISS: Prefilled pen: up to 0.47 mg/kg/week SC divided into six or seven doses Treatment of Noonan Syndrome: Prefilled pen: 0.46 mg/kg/week SC divided into six or seven doses Treatment of SGA: Prefilled pen: up to 0.47 mg/kg/week SC divided	Prefilled pen (Norditropin® FlexPro®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL 30 mg/3 mL Vial: 4 mg 8 mg

		into six or seven doses† Treatment of Prader-Willi Syndrome: Prefilled pen: 0.24 mg/kg/week SC divided into six or seven doses Treatment of Turner Syndrome: Prefilled pen: up to 0.47 mg/kg/week SC divided into six or seven doses	
Somatropin (Nutropin®)	Treatment of GHD in adults: Prefilled cartridge, prefilled pen cartridge: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase gradually every one to two months by increments of 0.1 to 0.2 mg/day based on response and serum IGF-1 concentrations, initial (weight-based), up to 0.006 mg/kg SC daily, increase according to response, adverse effects, and serum IGF-1 concentration; maximum of 0.025 mg/kg/day in patients ≤35 years old or 0.0125 mg/kg/day in patients >35 years old	Treatment of CKD: Prefilled cartridge, prefilled pen cartridge: up to 0.35 mg/kg/week SC divided into daily doses Treatment of GHD in pediatrics: Prefilled cartridge, prefilled pen cartridge: up to 0.3 mg/kg/week SC divided into daily doses Treatment of GHD in pubertal patients: Prefilled cartridge, prefilled pen cartridge: up to 0.7 mg/kg/week SC divided into daily doses Treatment of ISS: Prefilled cartridge, prefilled pen cartridge: up to 0.3 mg/kg/week SC divided into daily doses Treatment of Turner Syndrome: Prefilled cartridge, prefilled pen cartridge: up to 0.375 mg/kg/week SC divided into three to seven doses	Prefilled pen (Nutropin AQ NuSpin®): 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL
Somatropin (Omnitrope®)	Treatment of GHD in adults: Prefilled cartridge, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase gradually every one to two months by increments of 0.1 to 0.2 mg/day based on response and serum IGF-1	Treatment of GHD in pediatrics: Prefilled cartridge, vial, powder for reconstitution: up to 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Treatment of ISS: Prefilled cartridge, vial, powder for reconstitution:	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg/vial

	concentrations; initial (weight-based), up to 0.04 mg/kg/week, SC divided into daily doses, increase every four to eight week according to response, adverse effects, and serum IGF-1 concentration; maximum 0.08 mg/kg/week	up to 0.47 mg/kg/week SC divided into six or seven doses Treatment of Prader-Willi Syndrome: Prefilled cartridge, vial, powder for reconstitution: up to 0.24 mg/kg/week SC divided into six or seven doses Treatment of SGA: Prefilled cartridge, vial, powder for reconstitution: up to 0.48 mg/kg/week SC divided into six or seven doses Treatment of Turner Syndrome: Prefilled cartridge, vial, powder for reconstitution: up to 0.33 mg/kg/week SC divided into six or seven doses	
Somatropin (Saizen®)	Treatment of GHD in adults: Cartridge, powder for reconstitution, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.3 mg SC daily, increase every one to two months by increments of 0.1 to 0.2 mg/day based on clinical response, side effects, and serum IGF-1 levels, initial (weight based), 0.005 mg/kg SC daily, increase after four weeks based on clinical response, side effects, and serum IGF-1 levels; maximum, 0.01 mg/kg/day	Treatment of GHD in pediatrics: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.18 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses	Cartridge, powder for reconstitution (Click.Easy® or Saizenprep®): 8.8 mg Vial, powder for reconstitution: 5 mg/vial 8.8 mg/vial
Somatropin (Serostim®)	HIV-associated wasting or cachexia: Vial, powder for reconstitution: initial, 0.1 mg/kg SC daily at bedtime with the following weight-based dosage: body weight <35 kg, 0.1 mg/kg/day; 35 to 45 kg, 4 mg/day; 45 to 55 kg, 5 mg/day; >55 kg, 6 mg/day; maximum, 6 mg.	Safety and efficacy in children have not been established	Vial, powder for reconstitution: 4 mg 5 mg 6 mg
Somatropin	Treatment of GHD in	Treatment of GHD in	Vial, powder for

(Zomacton®)	adults: Vial, powder for reconstitution: initial (non-weight based) 0.15 to 0.3 mg SC daily, increase every one to two months by 0.1 to 0.2 mg/day according to response and serum IGF-1 concentrations, initial (weight-based), 0.006 mg/kg SC daily, increase based on response, adverse reactions, and serum ICF-1 concentration; maximum, 0.0125 mg/kg daily	pediatrics: Vial, powder for reconstitution: 0.18 to 0.3 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses Treatment of ISS: Vial, powder for reconstitution: up to 0.37 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses Treatment of SGA: Vial, powder for reconstitution: up to 0.47 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses† Treatment of short stature or growth failure in short SHOX deficiency: Vial, powder for reconstitution: 0.35 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses Treatment of Turner Syndrome: Vial, powder for reconstitution: up to 0.375 mg/kg/week SC divided into equal doses given on three alternative days or six or seven doses	reconstitution: 5 mg 10 mg

CKD=chronic kidney disease, FDA=US Food and Drug Administration, GHD=growth hormone deficiency, HIV=human immunodeficiency virus, HSDS=height standard deviation score, IGF-1=insulin-like growth factor, ISS=idiopathic short stature, IU=international unit, SC=subcutaneous, SGA=small for gestational age, SHOX=short-stature homeobox

* Initial treatment with larger doses of somatropin (e.g., 0.48 mg/kg/week) is recommended in very short children (i.e., HSDS <-3) and/or older/pubertal children. A reduction in dosage (e.g., gradually towards 0.24 mg/kg/week) should be considered if substantial catch-up growth is observed during the first few years of therapy. In pediatric patients less than four years of age with less severe short stature, baseline HSDS values between -2 and -3, consider initiating treatment at 0.24 mg/kg/week and titrate the dose as needed.

†In very short pediatric patients, HSDS less than -3, and older pubertal pediatric patients consider initiating treatment with a larger dose (up to 0.067 mg/kg/day). Consider a gradual reduction in dosage if substantial catch-up growth is observed during the first few years of therapy. In pediatric patients less than 4 years of age with less severe short stature, baseline height SDS values between -2 and -3, consider initiating treatment at 0.033 mg/kg/day and titrate the dose as needed.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the growth hormone agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with Growth Hormone Agents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Growth Failure Associated With Chronic Renal Insufficiency Before Renal Transplant				
Fine et al.[26] (1995) GH (Nutropin®) 0.05 mg/kg/day SC vs placebo The dose of GH was adjusted for change in weight at each 3-month visit. The following drugs were permitted to be administered routinely to all patients: multivitamins, vitamin D analog, calcium carbonate or aluminum hydroxide, sodium bicarbonate, prophylactic antibiotic therapy with sulfamethoxazole/ trimethoprim or	MC, PC, RCT Pediatric patients with irreversible renal insufficiency, creatinine clearance >5 and <75 mL/min/1.73m^2, short stature with height <3rd percentile for chronological age, bone age <10 years for girls and <11 years for boys and prepubertal status	N=30 2 years (treatment was discontinued at the time of renal trans-plantation or if significant adverse events occurred)	Primary: Growth, laboratory evaluations, renal function, adverse events Secondary: Not reported	Primary: The mean first year growth rate with GH was 14.1±2.6 cm/year compared to 9.3±1.5 cm/year with placebo (P<0.00005). The mean second year growth rates were 8.6±2.1 vs 6.9±1.0 cm/year (P=0.025). There was significant improvement in the mean height SDS with GH during the two years (-3.0 to -1.1; P<0.00005), whereas there was no change with placebo (-2.5 to -2.7; P value not reported). After two years, mean bone age increased by 2.1±0.6 and 1.4±0.2 years with GH and placebo (P<0.01). There was a significantly greater mean weight gain with GH compared to placebo (5.6±1.2 vs 4.0±0.9 kg; P=0.003). This was accompanied by a decrease in mean triceps skin-fold thickness with GH (-2.3±1.5 mm vs 0.2±3.3 cm; P=0.04). There was a significant difference between baseline and two year values for HbA1c (P=0.02) and creatinine (P=0.005) with placebo, and in IGF-1 (P=0.004), alkaline phosphatase (P=0.008), post-prandial insulin (P=0.007), post prandial glucose (P=0.02), HbA1c (P=0.03) and creatinine (P=0.017) with GH. Despite the increase in mean post-prandial insulin values with GH, there was no clinical evidence of glucose intolerance. Only IGF-1 (P=0.04) and post-prandial insulin (P=0.02) values were significantly different between placebo and GH for the change between baseline and two years. The mean increment in serum creatinine level from baseline to two years was 0.9 mg/dL (2.0±1.3 to 2.9±1.9; P=0.005) with placebo and 0.5 mg/dL (1.5±0.7 to 2.0±0.9; P=0.02) with GH. The mean estimated creatinine clearance with placebo declined from 21.9±9.7 to 18.8±9.2 mL/min/1.73 m^2 (P=0.12). The mean estimated creatinine clearance with GH declined from 30.9±10.9 to 30.6±13.1 mL/min/1.73 m^2 (P=0.92). During the two years the incidence of adverse events was similar with the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nitrofurantoin and antihypertensive medications other than clonidine. At the discretion of the investigator, treatment with recombinant human erythropoietin was also permitted.				two treatments. Due to the small sample size and low incidence of adverse events, statistical tests could not be applied. Secondary: Not reported
Santos et al.[27] (2010) GH (Norditropin®) 0.33 mg/kg/week daily SC vs no GH	MC, OL, PG, PRO, RCT Pediatric patients with a GFR ≤60 mL/min/1.73 m^2, length below -2 SDS for the same chronological age and growth velocity <50th percentile, conservative treatment or long term peritoneal dialysis, euthyroid status and nutritional intake providing a daily amount ≥80% of recommended daily allowances for calories and 10% of calories from high biologic value proteins	N=16 1 year	Primary: Growth, bone mass, hormonal determinations, safety Secondary: Not reported	Primary: Body length SDS increased throughout treatment with GH only. After one year, patients receiving GH gained 14.5±1.2 cm and 1.4±0.3 SDS compared to 9.5±1.1 cm and -0.1±0.3 SDS with patients not receiving GH (P=0.024 and P=0.031, respectively). Similar results were observed for weight SDS; however, results were not significant between the two treatments (P value not reported and P=0.18). Head circumference increased with both treatments, from 44.9±0.8 to 47.8±0.6 cm (P<0.001) with GH and from 45.3±0.8 to 47.5±0.6 cm (P<0.001) with no GH, without a difference between the two treatments (P value not reported). There was also no difference between the two treatments with regards to brachial circumference and forearm length (P values not reported). Bone area, BMC and BMI increased from the six month visit onward with GH. In patients receiving no GH, BMC and BMI became higher than baseline after six months, but the difference did not persist after one year. There were no differences between the two treatments at any time point. Total IGF-1 SDS increased significantly after three months of GH (from -0.85±0.13 to -0.22±0.12; P<0.05) and remained so throughout the trial (-0.08±0.16, 0.20±0.24 and 0.14±0.38 at months six, nine and 12, respectively). Total IGF-1 SDS did not change with no GH (-0.75±0.13 to -0.75±0.12, -0.86±0.16, -0.79±0.241 and -0.75±0.38 at baseline and months three, six, nine and 12). Free IGF-1 SDS increased significantly after nine and 12 months of GH treatment compared to baseline (0.64±0.52, 4.65±1.07, 3.50±0.93, 3.47±0.81 and 3.25±0.72 at baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and months three, six, nine and 12). IGFBP-3 SDS increased significantly until month nine (P<0.05) with GH from -0.22±0.40 to 1.26±0.38, 1.26±0.46, 1.18±0.47 and 0.77±0.51 at months three, six, nine and 12, respectively, whereas it did not change with no GH (0.04±0.40, 0.27±0.38, 0.19±0.46, 0.44±0.47 and 0.18±0.51, respectively). There were no differences in SDS IGFBP-I between the two treatments in basal and final visits; however, at months three, six and nine, levels were significantly higher with no GH (P values not reported). No consistent variations or differences between the two treatments were observed for IGF-2, IGFBP-2, GHBP, ghrelin or leptin (data not reported). Bone age advanced similarly with both treatments throughout the trial (0.98±0.10 and 0.98±0.12 years with GH and no GH, respectively). Basal and final bone age and bone age-chronological age ratios were not different between the two treatments. Blood pressure, hemoglobin, leukocyte and platelet counts, serum concentrations of sodium, bicarbonate, total proteins, albumin, transaminases, fasting glucose, HbA1c, insulin, T_4, TSH, ferritin, cholesterol and TG remained within the normal range throughout the trial with no differences between the two treatments. Serum concentrations of calcium phosphate, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and PTH were similar between the two treatments and did not change throughout the trial. There were 29 adverse events; nine with GH and 20 with no GH (P=0.065). None of the adverse events were considered to be treatment-related. Mild to moderate adverse events included acute respiratory infection, acute otitis media, chickenpox, abdominal pain and acute gastroenteritis. Serious adverse events occurring with both treatments included urinary tract infections and surgical procedures. Secondary: Not reported
Vimalachandra et al.[28] (2006) GH	SR (15 RCTs) Patients 0 to 18 years of age diagnosed with chronic kidney	N=629 Duration varied	Primary: Difference in mean change in height SDS between the treatment and control groups	Primary: GH vs control: The effect of GH compared to control on height SDS was reported in six trials. After one year, treatment with GH increased height (MD, 0.78; 95% CI, 0.52 to 1.04). In one trial, data were available for two years of treatment and most of the growth acceleration occurred during the first

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or no GH (control) OR RCTs that compared two doses of GH (28 IU/m^2/week vs 14 IU/m^2/week or 28 IU/m^2/week vs 58 IU/m^2/week)	disease who are predialysis, on dialysis or post-transplant		Secondary: Change in height SDS from treatment onset to completion, change in height velocity, change in height velocity SDS, change in bone age, other outcomes, adverse events	year of treatment, while treatment in the second year resulted in a small and nonsignificant increase in height SDS (MD, 0.37; 95% CI, -0.10 to 0.84). However, GH treatment for two years resulted in a persisting significant difference in height SDS between GH and control (MD, 1.36; 95% CI, 0.86 to 1.86). Secondary: GH 28 IU/m^2/week vs GH 14 IU/m^2/week: Two trials reported no difference in the change in height SDS between the two doses after one year (MD, 0.17; 95% CI, -0.14 to 0.49). One of the trials observed no differences between the two doses after six months (MD, 0.20; 95% CI, -0.33 to 0.73) and between six months and one year of treatment (MD, 0.12; 95% CI, -0.43 to 0.68). GH 28 IU/m^2/week vs GH 56 IU/m^2/week: One trial reported no difference in the change in height SDS between the two doses after one year (MD, 0.30; 95% CI, -1.00 to 1.06). GH vs control: The effect of GH compared to control on height velocity was reported in nine trials. Two trials reported an increase of 2.85 cm over six months (MD, 2.85 cm/six months; 95% CI, 2.22 to 3.48). Six trials reported an increase over one year of 3.80 cm/year (MD, 3.80 cm/year; 95% CI, 3.20 to 4.39). One trial reported results for the second year in which there was a greater decrease in height velocity with GH compared to control (MD, -1.90 cm/year; 95% CI, -3.04 to -0.76); however, height velocity with GH remained significantly higher compared to control during the second year of treatment (MD, 2.30 cm/year; 95% CI, 1.39 to 3.21). GH 28 IU/m^2/week vs GH 14 IU/m^2/week: Three trials combined in a MA showed a significant increase in height velocity with 28 IU/m^2/week (MD, 1.34 cm/year; 95% CI, 0.55 to 2.13). One trial reported an increase in height velocity to six months with 28 IU/m^2/week (MD, 1.96 cm/six months; 95% CI, 0.86 to 3.05), which waned during the second six months of treatment (MD, -0.53 cm/six months; 95% CI, -1.65 to 0.59). Another trial reported a 2.7 cm/year (14 IU/m^2/week) and a 2.6 cm/year (28 IU/m^2/week) increase in height

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				velocity (P<0.05). GH 56 IU/m^2/week vs GH 28 IU/m^2/week: One trial reported no difference in mean height velocity after one year (MD, 1.10 cm/year; 95% CI, -1.30 to 3.50). GH vs control: The effect of GH compared to control on height velocity SDS was reported in three trials. Two reported an increase in height velocity SDS over six month (MD, 7.80; 95% CI, 6.09 to 9.51) and one reported an increase over one year (MD, 6.14; 95% CI, 3.41 to 8.86). GH 28 IU/m^2/week vs GH 14 IU/m^2/week: Among three trials, height velocity SDS at one year was significantly higher with GH 28 IU/m^2/week (MD, 1.48; 95% CI, 0.03 to 2.93). Height velocity SDS was significantly increased with GH 28 IU/m^2/week at six months (MD, 2.05; 95% CI, 0.82 to 3.28) but no between six months and one year (MD, -0.65; 95% CI, -2.09 to 0.80). GH vs control: The effect of GH compared to control on bone age was reported in six trials. There was no difference in the change in bone age between the two treatments over six months (MD, -0.15; 95% CI, -1.77 to 1.48), one year (MD, 0.16; 95% CI, -0.72 to 1.03) or between one and two years of treatment (MD, 0.40; 95% CI, -0.99 to 1.79). GH vs control: The effect of GH compared to control on kidney function was reported in nine trials and all reported that kidney function did not differ between the two treatments. Two trials reported data on lipids and found no difference in cholesterol, TGs, apo; however, Lp(a) levels were significantly higher with GH. Three trials reported data on glucose tolerance and no significant differences were observed between GH and control.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Reported side effects included asthma/wheezing, acute rejection in transplantation, deterioration in kidney function, raised fasting glucose, papilledema, glucose intolerance, granuloma formation, lymph node swelling, claudication, hypertension and worsening of pre-existing idiopathic scoliosis. Only one trial demonstrated a significant increase in adverse events with GH compared to control.
Growth Failure Associated With Noonan Syndrome				
Noordam et al.[29] (2001) GH 0.15 IU/kg/day SC Eight patients immediately started GH and after 2 years, discontinued treatment for 1 year (Group A). Fifteen patients served as a control group during the first year and started GH after 1 year and received GH for 2 years (Group B). An additional 14 patients were treated with GH for 3 years (Group C).	MC, RCT Pediatric patients with Noonan syndrome with height SDS below -2 and eligible to receive GH	N=37 3 years	Primary: Height SDS, mean bone maturation, effect of discontinuing and restarting GH in Group A Secondary: Not reported	Primary: Gain in height SDS over the first year was significantly higher with GH (Groups A+C) compared to no GH (Group B) (0.5±0.14 vs 0.0±0.2; P<0.05). Over the second year the gain in height SDS in Group B was comparable with the first year response in Groups A+C (0.5±0.5 vs 0.5±0.4; P value not reported). At the two year follow up, the mean changes in height SDS were no different between Groups A+C and B (0.8 vs 0.5; P value not reported). Over the first year, the gain in height SDS for bone age was not different between Groups A+C and B. This finding was caused by the significantly lower rate of bone maturation in the first year of the trial in Group B. The effect of the first year of GH treatment on bone maturation was similar in Groups A+C and B (1.2±0.5 vs 1.2±0.9; P value not reported). Gain in height SDS over three years was not different between Groups A and B (0.8±0.7 vs 0.8±0.5; P value not reported). The change in height SDS for bone age over three years was significantly different; a decrease was observed with Group A (-0.7 vs 0.3; P value not reported). Over three years, bone maturation was accelerated with Group A compared to Group B (1.3 vs 0.9; P<0.05). Over the third year of the trial alone, "catch-down" growth was seen in Group A, which was reflected by the significantly lower mean change in height SDS compared to Group B (-0.2 vs 0.2; P<0.05). Secondary: Not reported
Horikawa et al.[30] (2020)	DB, MC, OL, PG, RCT	N=51 4 years	Primary: Change in height SDS from baseline	Primary: After 104 weeks, the mean height SDS based on Japanese national reference data for children increased from -3.24 at baseline to -2.40 in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin (Norditropin®) 0.033 mg/kg SC once daily vs Somatropin (Norditropin®) 0.066 mg/kg SC once daily	Japanese children (males aged three to below eleven years of age, females aged three to below ten years of age) with Noonan syndrome with -2 height SDS or below		to 104 weeks of treatment based on Japanese national reference data Secondary: Change in height SDS from baseline to 208 weeks of treatment based on Japanese national reference data for children or on reference data from Japanese Noonan syndrome patients	0.033 mg/kg/day group and from -3.25 to -1.78 in the 0.066 mg/kg/day group. Secondary: After 208 weeks, the mean height SDS based on the Japanese national reference data for children increased from -3.24 at baseline to -2.39 in the 0.033 mg/kg/day group and from -3.25 to -1.41 in the 0.066 mg/kg/day group. After 208 weeks, the mean gain in height SDS based on data from Japanese Noonan syndrome patients was 0.96 (95% CI: 0.74 to 1.18) in the 0.033 mg/kg/day group and 1.91 (95% CI: 1.70 to 2.12) in the 0.066 mg/kg/day group.
Growth Failure Associated With Prader-Willi Syndrome				
Bakker et al.[31] (2015) GH (Genotropin®) 1 mg/m^2/day SC vs no treatment	MC, RCT Patients aged 6 to 12 years old (girls) or 6 to 14 years old (boys) with genetically confirmed diagnosis of PWS	N=153 2 years	Primary: Health-Related Quality of Life (HRQOL) questionnaires Secondary: Not reported	Primary: Children filled out their questionnaire separately from their parents, under supervision of a psychologist. When completed by the child, GH-treated children showed a significant improvement on the HRQOL in the Physical subdomain of the Dutch Children AZL/TNO Questionnaire Quality of Life short form (DUX25) and the DUX Prader Willi (DUXPW) compared to the untreated children (P<0.05 and P<0.001, respectively). Parents of GH-treated children reported a significant improvement in HRQOL in the Physical and Emotional subdomains of the DUX25 compared to parents of untreated children (P<0.01 and P<0.05, respectively). Parents reported no significant differences between GH-treated children and untreated children in the DUXPW, and subdomains Home and Social of the DUX25. Secondary: Not reported
Bakker et al.[32] (2015)	MC, OL, RCT Prepubertal patients	N=73 2 years	Primary: Energy intake, anthropometric	Primary: Mean baseline energy intake of children with PWS was significantly lower compared to daily energy requirements for age- and sex-matched healthy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Genotropin®) 1 mg/m^2/day SC vs no treatment	aged six months to 12 years old (girls) or six months to 14 years old (boys) with genetically confirmed diagnosis of PWS		measurements, body composition, resting energy expenditure Secondary: Not reported	children in the GH treated and untreated groups (P<0.001). After one year of study, infants had no significant difference in energy intake versus daily energy requirements between the GH group and the untreated group. In the prepubertal children, there were also no difference between the GH group and the untreated group after two years. After one year, the median increase in energy intake in the GH group was higher than in the untreated group, 264 versus 108 kcal/day (P=0.072). The GH group demonstrated a non-significant increase in energy intake whereas children of the untreated group had a non-significant decrease in energy intake after two years compared to baseline, but no significant difference was observed in the change in energy intake between the GH and untreated group. After two years, the total energy intake was not significantly different between the GH group and untreated group, 1,272 versus 1,156 kcal/day (P=0.064). After one year, fat percentage remained stable in the GH group while it increased in the untreated group (P=0.036). After two years, the fat percentage SD score decreased during GH treatment (P=0.002) and increased in the untreated group (P=0.003) compared to baseline. Resting energy expenditure significantly increased in both the GH group and the untreated group (P=0.003 vs P<0.001, respectively), but it was not significantly different between the groups. In the untreated group, there were no correlations found with lean body mass (P=0.257 for infants and P=0.791 for prepubertal children) or fat percentage (P=0.847 for infants and P=0.411 for prepubertal children). Increase in energy intake during two years of GH treatment was correlated with lower fat percentage SD scores (P=0.037) and higher adiponectin levels (P=0.007) Secondary: Not reported
Kuppens et al.[33] (2017)	DB, PC, RCT, XO Patients treated with	N=27 2 years	Primary: Components of metabolic syndrome	Primary: GH treatment resulted in similar glucose and insulin levels compared to placebo during OGTT. Only fasting glucose and insulin levels were higher

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Genotropin®) 0.67 mg/m^2/day vs placebo Subjects received one year of GH treatment or one year of identical appearing placebo, after which they crossed over to the alternative treatment for another year. Patients were prescribed GH during childhood at an initial dose of 1 mg/m^2/day and was lowered due to high serum IGF-1 levels	GH for at least two years that attained adult height with genetically confirmed PWS		including carbohydrate metabolism (fasting blood levels of glucose and insulin measured by OGTT), blood pressure, TC, LDLc, HDLc, TG, IGF-1 and IGFBP-3 SDS Secondary: Not reported	after GH treatment compared with placebo (P=0.012 and P=0.037, respectively). GH treatment resulted in similar systolic and diastolic blood pressure (P=0.547 and P=0.779, respectively) when compared to placebo. Compared to placebo, GH treatment resulted in similar levels of TC, LDLc, HDLc, and TG (P=0.851, P=0.711, P=0.974, and P=0.415, respectively). After one year of GH treatment, four patients had central obesity, three patients had low HDLc levels, and five patients had high blood pressure. After one year of placebo, five patients had central obesity, one patient had high TG levels, six patients had low HDLc levels, four patients had high blood pressure, and one patient had a high fasting glucose. Compared to placebo, GH treatment did not result in metabolic syndrome. IGF-1 and IGFVP-3 SDS had a mean difference of 2.5 and 1.0 between GH and placebo (P<0.001). Secondary: Not reported
Kuppens et al.[34] (2016) GH (Genotropin®) 0.67 mg/m^2/day vs placebo Subjects received one year of GH treatment or one	DB, PC, RCT, XO Patients treated with GH for at least two years that attained adult height with genetically confirmed PWS	N=27 2 years	Primary: Body composition Secondary: Safety and adverse events	Primary: Compared with placebo, GH treatment resulted in a lower mean fat mass (mean difference, -2.9;, P=0.004) and higher lean body mass (mean difference, 1.5; P=0.005). Compared with placebo, GH treatment decreased fat mass percentage of limbs and trunk by 4.7% and 3.3%, respectively) (P<0.001 and P=0.007). Concurrent with the GH dose reduction from 0.88 mg/m^2/day (mean administered GH dose at prior to study), IGF-1 SDS decreased from 2.2 SDS at baseline to 1.7 during the GH year (P=0.124). Fat mass percentage increased in the group where the GH dose was lowered from 0.88 at baseline to 0.67 mg/m^2/day in the first year (P=0.018) and lean body mass

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
year of placebo, after which they crossed over to the alternative treatment for another year. Patients were prescribed GH during childhood at an initial dose of 1 mg/m^2/day and was lowered due to high serum IGF-1 levels				remained stable (P=0.122). After the two-year study, 88.9% of subjects underwent an arginine-growth hormone releasing hormone test. Only 12.5% had a GH peak below the BMI-dependent cut-off. There was no significant effect of the GH peak on the effects of GH versus placebo treatment on fat mass percentage, fat mas, or lean body mass (P=0.649, P=0.170, and P=0.093, respectively). Secondary: Compared with placebo, GH treatment resulted in higher mean fasting glucose and insulin (P=0.012 and P=0.037, respectively). None of the patients developed type 2 diabetes mellitus. IGF-1 and IGFBP-3 SDS were significantly lower during placebo than during GH (P<0.001 for both). Systolic and diastolic BP were similar in both treatment phases. No serious adverse events were considered to be related to GH. During GH, seven adverse events occurred, all were viral respiratory tract infections. During placebo, there were two serious adverse events and 12 adverse events including one patellar luxation, one knee rotation, and ten viral respiratory tract infections.
Reus et al.[35] (2014) GH (Genotropin®) 1 mg/m^2/day SC vs GH (Genotropin®) 1 mg/m^2/day SC started after an initial control period The control period was originally defined as 12 months; however, this was shortened to	RCT, SB Patients up to the age of 36 months with PWS	N=22 2 years	Primary: Muscle measurement, strength, and motor performance Secondary: Not reported	Primary: After six months, the forearm flexors were significantly thicker in the GH than in the control group (P<0.05) Muscle thickness in the GH group had improved significantly in the biceps brachii, forearm flexors, and tibialis anterior compared to baseline; and in the control group only the muscle thickness of the tibialis anterior had improved. After 12 months of GH treatment, the muscle thickness in the forearm flexors and quadriceps was significant improved (P<0.05 for both muscle groups). All four muscle groups showed a significant positive effect of GH on muscle thickness when controlled for age and baseline muscle thickness. Decreased muscle thickness in specific muscle groups is strongly associated with decreased muscle strength and motor performance as evidenced by the correlation between muscle thickness and muscle strength, muscle thickness and motor development, and muscle strength and motor development (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
six months based on results of study that revealed effectiveness of GH				Secondary: Not reported
Carrel et al.[36] (1999) GH (Nutropin®) 1 mg/m^2/day SC vs no GH (control)	RCT Pediatric patients with PWS	N=54 1 year	Primary: Growth and GH axis, body composition, BMD, energy expenditure, strength and agility, pulmonary function, lipids, carbohydrate metabolism, scoliosis, other adverse events Secondary: Not reported	Primary: After one year, height increased by 10.1±2.5 cm with GH and was accompanied by an increase in growth velocity SDS from -1.1±2.5 to 4.6±2.9 (P<0.001). Height increased by 5.0±1.8 cm with control and was accompanied by an increase in growth velocity SDS from -0.9±1.7 to -0.7±1.9 (P value not significant). Mean IGF-1, osteocalcin and type 1 procollagen levels increased significantly with GH (P<0.01 vs baseline and control). Mean bone age progressed with control; 1.4 years compared to 1.5 years with GH (P value not significant). After one year, body fat decreased by eight percent overall (46.3±5.8 to 38.4±10.7%; P<0.01) with GH compared to no change with control. LBM increased with GH (to mean of 25.6±4.3 kg; P<0.01) and remained unchanged with control. After one year, femoral head BMD increased by 0.9±0.2 g/cm^2 with GH (P<0.05 vs baseline and control). GH was also associated with nonsignificant increases in lumbar spine and total body BMD. After one year, resting energy expenditure was not significantly increased with GH; however, respiratory quotient values decreased (0.81±0.07 to 0.77±0.05; P<0.0001). Values remained unchanged with control. After one year, GH improved the agility run (faster by 2.3±0.5 seconds), broad jump (farther by 3.3±1.9 inches), abdominal strength (an improvement of 3.0±2.1 sit ups/20 seconds) and upper extremity strength (increase of 2.5±1.8 weight-lift repetitions/30 seconds) (P<0.01 vs baseline and control). Increases in both inspiratory (45.8±4.1 to 55.7±13.7 cm/H_20; P<0.001) and expiratory (54.6±7.1 to 69.3±20.8 cm/H_20; P value not reported) muscle forces occurred only with GH.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				After one year, mean TC decreased from 184 to 166 mg/dL, mean HDL-C increased from 42 to 50 mg/dL and mean LDL-C decreased from 125 to 106 mg/dL with GH (P<0.01 for all). No changes were seen with control. After one year, both fasting and two- hour mean insulin levels increased slightly, but not significantly with GH (P=0.09). After one year, mean curvature was 16 and 12 degrees with control and GH (P value not significant). Headaches occurred in two patients within the first three weeks of GH treatment. In both cases symptoms resolved with temporary cessation and gradual reinstitution of GH. Ophthalmologic examination of one child failed to reveal evidence of pseudotumor cerebri. Secondary: Not reported
Myers et al.[37] (1999) GH (Nutropin®) 1 mg/m^2/day SC vs no GH (control) All patients were observed for 6 months prior to randomization.	RCT Patients 4 to 16 years of age with genetically confirmed PWS	N=44 1 year	Primary: Height, IGF-1, bone age, body composition, energy expenditure, physical performance, adverse events Secondary: Not reported	Primary: After one year, the mean height increased by 10.0±2.5 cm, with a height velocity SDS of 4.6±2.9 (P<0.001) with GH. After one year, mean IGF-1 levels increased to 522±127 ng/mL with GH (P<0.01). There was no difference in bone age progression between the two treatments (P value not reported). After one year, percentage body fat decreased significantly by 16% to 38.4±10.7% (P<0.0001) and LBM increased significantly (P<0.0001) with GH. Femoral neck BMD increased significantly (P<0.05) with GH, and there were nonsignificant increases in total body and lumbar spine BMDs. Although resting energy expenditure did not change significantly after one year of GH, respiratory quotient decreased from 0.81±0.07 to 0.77±0.05 (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Physical performance improved significantly with GH in the timed run, standing broad jump, sit up and arm curl exercises compared to baseline and control (data not reported). Significant increases in respiratory muscle forces, both inspiratory (from 45.8±4.1 to 55.7±13.7 cm/H_20; P<0.001) and expiratory (from 54.6±7.1 to 69.3±20.8 cm/H_20; P value not reported) occurred after a year of GH. Adverse events with GH were rare. There were no differences in the progression of scoliosis between the two treatments. Headaches occurred in two patients within three weeks of initiating GH but resolved after the temporary cessation and gradual reinstitution of GH. Both fasting and two hour insulin levels increased with GH; however, the changes were not significant. Mean free T_4 levels did not change significantly with GH. Secondary: Not reported
Lindgren et al.[38] (1998) GH (Genotropin®) 0.1 IU/kg/day SC vs no GH (control)	MC, RCT Patients 3 to 12 years of age with PWS	N=29 1 year	Primary: Growth and GH axis, body composition, bone age, laboratory parameters, BMD, progression to puberty Secondary: Not reported	Primary: Significant changes were observed in height, height velocity, BMI and IGF-1 levels with GH (P<0.001 for all). Body composition revealed an average of a 25% reduction in fat mass and a 30% increase in fat-free mass with GH (P<0.001 for both). Muscle and fat area of the thigh showed similar results. There were no differences between the two treatments with regards to the progression of bone age during the trial (P value not reported). After one year, IV glucose tolerance tests were normal and unchanged with GH; however, basal fasting insulin levels were significantly increased (from 10.4±2.7 to 19.2 mU/L±10.5 SD; P<0.001). There were no significant changes in HbA1c with either treatment (P value not reported). There was no severe progression of scoliosis with either treatment. The BMD did not differ between the two groups either (P value not reported). No difference between the two treatments was observed in the progression of puberty. The only sign of puberty observed was pubic hair.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Carrel et al.[39] (2004) GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control)	RCT Pediatric patients with genetically confirmed PWS	N=29 1 year	Primary: Growth and GH axis, body composition, energy expenditure, mobility and stability, carbohydrate and lipid metabolism, adverse events Secondary: Not reported	Primary: After one year, there was an increase in height of 15.4±2.3 and 9.2±3.2 cm with GH and control (P<0.001). GH was accompanied by an increase in growth velocity SD from 1.4±1.8 to 5.0±1.8 (P<0.001), whereas with the control group it remained unchanged (1.2±1.4). GH was associated with a significant improvement in IGF-1 compared to control (231±98 vs 51±28 ng/mL; P<0.001). There were no differences in mean bone age progression between the two treatment groups. After one year, body fat decreased 4.8±5.7% with GH compared to 4.1±4.6% with control (P=0.001). LBM increased significantly more with GH (3.6±0.5 vs 1.8±0.7 kg; P<0.001). No significant changes were observed in total body BMD, which increased 14.1±10.4 and 9.0±6.9% with GH and control (P value not significant). After one year, total energy expenditure significantly increased with GH from 663±149 to 1,025±174 kcal/day compared to 697±124 to 945±341 kcal/day with control (P<0.05 vs baseline and control). When the entire cohort is examined, no effect of GH on mobility or stability skill acquisition was observed. After one year, no difference in fasting insulin was observed between the two treatments (5.6±7.1 vs 5.7±7.1 IU/mL; P value not significant). TC decreased from 163±34 to 159±40 mg/dL with GH and increased from 170±30 to 183±43 mg/dL (P value not significant). No differences were observed after one year of GH with regards to HDL-C, LDL-C and TGs (P values not reported). No changes in the prevalence of scoliosis were seen between the two treatments. No other adverse events were noted during the trial. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hauffa BP (abstract)[40] (1997) GH 0.15 IU/kg/day SC vs no GH (control)	RCT Pediatric patients with PWS with a short projected final height	N=17 1 year	Primary: Height, IGF-1 and IGFBP-3, body composition Secondary: Not reported	Primary: After one year, height velocity was significantly increased with GH (5.50 SD) compared to reference values for normal healthy pediatric patients, and decreased with control (-2.30 SD). The difference in height velocity between the two treatments was significant (P=0.0012). A gain in height was noted for chronological age (1.07 SD) after one year of GH and height gain remained unchanged (1.02 SD) when analyzed in relation to bone age. IGF-1 and IGFBP-3 increased significantly with GH (P<0.008). No differences between the two treatments were noted for parameters of weight and body composition. Secondary: Not reported
Festen et al.[41] (2008) GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control) After stratification for age, infants were randomized to GH treatment or no GH treatment for 1 year; in the second year, all infants received GH. After stratification for BMI, patients >3	RCT Patients 6 months to 14 years of age with genetically confirmed PWS, bone age <14 years for girls and <16 years for boys and prepubertal at the start of the trial	N=91 1 (infants) or 2 years (children >3 years of age)	Primary: Anthropometry, body composition (only children >4 years of age), IGF-1, IGFBP-3 Secondary: Not reported	Primary: For infants, median height SDS increased significantly after one (P<0.001) and two years (P<0.005) with GH. After two years of GH, all infants had a height SDS above -2. With the control group, median height SDS remained low in the first year, but increased significantly when GH was started in the second year (P<0.01). Median head circumference SDS increased accordingly (GH, one year; P<0.005 and two years; P<0.005 and control, one year; P<0.05 and two years; P<0.01). BMI SDS increased progressively with GH and control, but remained within the normal range for most patients (GH, two years; P<0.05 and control, one year; P<0.01 and two years; P<0.05). For patients greater than three years of age, median height SDS increased significantly compared to baseline after one (P<0.001) and two years (P<0.001) of GH treatment. With the control group, height SDS remained low. BMI SDS decreased significantly during the first year (P<0.001) of GH treatment and then stabilized at a level that was not significantly higher than 0 SDS (P=0.08 and P=0.12 after one and two years). With the control group, BMI remained significantly higher than 0 SDS. Head circumference increased significantly to normal values during GH treatment (two years; P<0.005), with tibia length (P<0.05), foot length

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
years of age were randomized to GH treatment or no treatment for 2 years.				(P<0.005), arm span (P<0.05) and sitting height (P<0.001) significantly improving, but remaining significantly lower than 0 SDS. For patients greater than three years of age, median LBM corrected for age SDS increased significantly with GH from -1.7 to -0.5 after one year (P<0.005), and to -0.1 (P value not reported) after two years, resulting in a LBM corrected for age not significantly below 0 SDS after one and two years of GH treatment. With the control group, LBM corrected for age SDS significantly decreased over time from -1.9 to -2.5 after two years (P<0.005) and body fat percentage remained high. LBM corrected for height and sex SDS did not significantly increase with GH (from -1.7 to -1.5 to -1.9 after two years; P value not reported). With the control group there was a progressive and significant decrease in LBM corrected for height and sex SDS (from -1.4 to -1.9 to -2.3), resulting in a significantly different change in LBM corrected for height and sex between GH and control after one (P<0.05) and two years (P<0.005). Median body fat percentage SDS decreased significantly from 2.1 to 1.5 to 1.9 at two years (P<0.005) but body fat percentage was still significantly higher than 0 SDS after one and two years of GH. Trunk fat decreased significantly in the first year (P<0.001) of GH and increased in the second year to a level still significantly below baseline (P<0.005). With the control group, trunk fat increased gradually, resulting in significantly higher levels after two years (P<0.05). For infants, IGF-1 increased with GH to a median above 2 SDS. After one year of GH, eight of 12 infants (67%) had an IGF-1 level >2 SDS, and after two years, it was five of seven infants (71%). With the control group, IGF-1 increased only during the second year. IGFBP-3 levels increased during GH treatment, but remained low during the first year with the control group. The IGF-1:IGFBP-3 ratio increased from -0.9 to 2.4 after two years of GH treatment (P=0.056) and from -0.3 to -1.1 after one year with no GH treatment to 2.5 after one year of GH treatment (P=0.056) in the control group. For patients greater than three years of age, after one year of GH, IGF-1 SDS had significantly increased (P<0.001) and remained high. After two years, 17 of 19 patients (89%) had IGF-1 SDS levels above 2. IGF-1 SDS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				remained low with the control group, with levels below 0 SDS during two years. Treatment with GH increased IGFBP-3 (one year; P<0.001 and two years; P<0.001), but not to the same SDS as IGF-1. Secondary: Not reported
Myers et al.[42] (2007) GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control) Patients randomized to no GH received no treatment for the first year and then were initiated on GH (Genotropin®) 1.5 mg/m^2/day SC. Data collected for these patients at 2 years are not presented within the article.	RCT Pediatric patients with genetically confirmed PWS	N=25 2 years	Primary: Growth and GH axis, body composition, motor development, language and cognitive skills, adverse events Secondary: Not reported	Primary: Mean length/height SDS normalized after one year of GH (-1.6±1.2 to -0.2±1.5; P<0.005) compared to a mean value of -1.5±0.7 (from -1.3±1.1) with control. GH also resulted in significantly greater growth in head circumference over the first year (-0.9 to -0.1 vs -0.5 to -0.2 SDS; P<0.01 vs control). IGF-1 increased significantly from 34±21 ng/mL at baseline to 231±98 and 319±106 ng/mL after one and two years of GH (P values not reported). The percent increase in LBM after one and two years of GH was 69 (P<0.005) and 30% (P value not reported), respectively, compared to 23% with control after one year (P value not reported). GH resulted in a significant decrease in percent body fat during the first year (P<0.005), followed by an increase during the second year (P value not reported). A trend towards improved mobility and stability percentile rankings were noted with GH (P values not reported). Patients receiving GH progressed significantly more during the first year of treatment in both language (P=0.05) and cognitive development (P=0.02) compared to those receiving no treatment. The only potential adverse event noted was scoliosis progression from 28 to 57 degrees despite bracing in one patient receiving GH, resulting in spinal rod placement. No patient required thyroid hormone replacement therapy. Secondary: Not reported
Carrel et al. (abstract)[43]	RCT	N=46	Primary: Height, body	Primary: Further changes in body composition, including decrease in fat mass and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2001) GH 0.3 to 1.5 mg/m^2/day SC All patients previously received GH 1 mg/m^2/day for 2 years.	Pediatric patients with PWS	1 year (3 years total)	composition, energy expenditure, BMD, strength and agility Secondary: Not reported	increase in LBM, growth velocity and resting energy expenditure were occurred with standard (1.0 mg/m^2/day) and higher doses (1.5 mg/m^2/day), but not with lower doses (0.3 mg/m^2/day). Prior improvements in BMD and strength and agility were sustained during the additional year of GH, regardless of dose. Secondary: Not reported
Lindgren et al. (abstract)[44] (1997) GH 0.1 IU/kg/day SC for 2 years (Group A) vs GH 0.2 IU/kg/day SC for 1 year (Group B) Patients in Group B received no GH treatment for the first year of the trial.	RCT Pediatric patients with PWS	N=27 2 years	Primary: Height, body composition Secondary: Not reported	Primary: Height velocity SDS increased from -1.9±2.0 to 6.0±3.2 during the first year of treatment in Group A and from -1.4±1.2 to 10.1±3.9 during the year of treatment in Group B. When GH was stopped, height velocity declined dramatically. Height SDS followed a similar pattern. GH reduced the percentage body fat and increased the muscle area of the thigh. Isometric muscle strength was also increased. GH appeared to have psychological and behavioral benefits, which were reversed after treatment was discontinued. Secondary: Not reported
Lindgren et al.[45] (1999) GH 0.1 IU/kg/day SC Patients were originally enrolled in Lindgren et al (abstract).	ES of Lindgren et al[33] Pediatric patients with PWS	N=18 5 years	Primary: Height, body composition, laboratory parameters Secondary: Not reported	Primary: After five years, mean height SDS exceeded ±0 SDS in all patients. Four of the patients reached their final heights (range, -1.1 to 0.9 SDS), which were within ±2 SD of their target heights. During the six months of observation only, BMI SDS increased significantly in patients who had only received GH for one year and remained unchanged in those who received GH for two years. During the following years of GH treatment, mean BMI SDS has remained unchanged for all patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
At the end of two years, all patients were observed for a period of 6 months and then restarted on GH 0.1 IU/kg/day SC for up to 5 years of total treatment.				After re-initiation of GH, patients who received GH for two years had fasting insulin levels within the normal range, while three patients who received GH for only one year developed hyperinsulinemia. Two of these patients developed non-insulin-dependent diabetes after a rapid weight gain, probably due to poor dietary compliance. BMI increased from 2.0 to 3.7 SDS and from 5.9 to 7.1 SDS in these two patients. Since discontinuation of GH, their fasting glucose, insulin and HbA1c levels have normalized. Secondary: Not reported
Bakker et al.[46] (2013) GH (Genotropin®) 1 mg/m^2 SC QD	MC, PRO Pediatric patients with Prader-Willi syndrome	N=60 8 years	Primary: Long-term effect of GH treatment on body composition Secondary: Assess efficacy of GH treatment (effect on height, BMI, head circumference, anthropometric data, and bone age), and to assess the safety of GH treatment (effect on blood pressure, fasting serum IGF-1, IGF binding protein 3, glucose homeostasis, and serum lipids	Primary: Mean LBM was low at baseline (−2.54 ± 0.18 SDS) but increased significantly (P<0.0001) during the first year of GH treatment. In the subsequent seven years of GH treatment, LBM remained very stable and without significant changes over time. After eight years of treatment, LBM SDS was still in the low to normal range and higher than at baseline (−1.5 ± 0.2 SDS, P<0.0001). During the first year of GH treatment, mean percent fat decreased significantly (P<0.0001). After the first year of GH treatment, percent fat gradually increased over the subsequent seven years; after eight years, it was, however, not significantly different from baseline (2.30 ± 0.10 SDS, P=0.06). After four years of GH treatment, the association of IGF-1 with LBM SDS was significant (β=0.34; P=0.02), but no association was found with percent fat SDS. After eight years of treatment, there was no association of IGF-1 SDS with LBM SDS (P=0.19) and percent fat SDS. Secondary: Although mean BMI SDS decreased slightly during the first year of GH treatment, BMI SDS remained stable in the subsequent seven years, and after eight years, it was not significantly different from baseline BMI SDS (P=0.14). Compared with PWS references, however, the mean BMIPWS decreased significantly from −0.49 ± 0.11 SDS to −0.84 ± 0.11 SDS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P<0.0001) during the first year of treatment. This positive effect persisted during the entire study period. As a result, the BMI PWS after eight years of GH treatment was −1.01 ± 0.13 SDS, which was significantly lower than at baseline (P<0.0001). During the first four years, height SDS normalized. Baseline mean height improved significantly from −2.24 ± 0.15 SDS to −0.08 ± 0.15 SDS (P<0.0001). In the subsequent four years of treatment, it remained stable. After eight years, height SDS was not significantly different from that in Dutch reference children (P=0.38). Mean head circumference SDS increased significantly during the first year of GH treatment (P<0.0001). The size after eight years of treatment was not significantly different from that in Dutch reference children (P=0.74). Mean IGF-1 increased during the first year of treatment, from −1.83 ± 0.17 SDS to 2.36 ± 0.12 SDS (P<0.0001). After the first year, IGF-1 SDS levels decreased to 2.11 ± 0.13 SDS at four years of treatment. On average, the IGF-1 levels were just above two SDS; after eight years of treatment, they were not significantly higher than two SDS (P=0.42). Mean IGFBP-3 increased significantly during the first year of GH treatment from −2.28 ± 0.18 to 0.49 ± 0.13 (P<0.0001) and remained so in the subsequent seven years. After eight years of treatment, IGFBP-3 was still significantly higher than at baseline (P<0.0001). The IGF-1/IGFBP-3 M ratio increased significantly during the first year of treatment (P<0.0001). Thereafter, the ratio stabilized, resulting in a mean of 0.40 ± 0.01 after eight years of treatment. During the first year of GH treatment, insulin increased significantly (P=0.031). After eight years of GH treatment, fasting insulin was not significantly higher than after one year of treatment (P=0.40) but was still significantly higher than at baseline (P=0.006). Like fasting insulin, HOMA-IR increased significantly in the first year of treatment (P=0.031) but remained stable and after eight years was not significantly different from that at one year of treatment (P=0.41). During GH treatment, mean fasting glucose levels gradually increased

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from 4.50 ± 0.07 mmol/L at baseline to 4.81 ± 0.05 mmol/L after eight years of treatment (P<0.001). None of the children developed type 2 diabetes mellitus. One Caucasian girl developed type 1 diabetes mellitus after 36 months of GH treatment. She had no positive family history for type 1 DM or autoimmune diseases. Percent fat SDS had a significant association with fasting insulin levels (β=2.25; 95% CI, 1.05 to 3.45, P<0.0001) and with HOMA-IR (β=0.42; 95% CI, 0.14 to 0.70, P=0.003) but had no significant association with fasting glucose levels (P=0.08). During eight years of GH treatment, TC and LDL levels decreased significantly compared with baseline (P=0.005 and P<0.0001, respectively). HDL levels did not change significantly during GH treatment (P=0.13). Percent fat SDS was significantly associated with HDL levels (β=−0.09; 95% CI, −0.17 to −0.02, P=0.017) but had no significant associations with TC levels and LDL levels. After eight years of GH treatment, systolic blood pressure SDS decreased significantly compared with baseline (P<0.05). Diastolic blood pressure SDS did not change during eight years of treatment (P=0.64). Before GH treatment, bone age was delayed, with a mean bone age/chronological age ratio of 0.79 (0.034) (P<0.0001, compared with 1). During the subsequent seven years of GH treatment, the BA/CA ratio was not significantly different compared with 1 (P=0.129).
Growth Failure Associated With Short-Stature Homeobox-Containing Gene Deficiency				
Blum et al.[47] (2007) Somatropin (Humatrope®) 50 µg/kg/day vs	MC, OL, RCT Patients ≥3 years of age with SHOX-D and prepubertal with height <3rd percentile of the local reference	N=52 (SHOX-D N=26 (TS) 2 years	Primary: Effect of somatropin on first year height velocity Secondary: Treatment effect in SHOX-D patients	Primary: Somatropin-treated SHOX-D patients had a significantly greater first year height velocity compared to untreated SHOX-D patients (P<0.0001). Secondary: There was no significant difference in first year height velocity in the somatropin-treated SHOX-D patients compared to somatropin-treated TS patients (P=0.592).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
no treatment vs somatropin (Humatrope®) 50 µg/kg/day in patients with TS	range or <10th percentile with height velocity <25th percentile, bone age <10 years for boys and <8 years for girls, no GHD, chronic disease and no known growth-influencing medications		compared to TS patients	There were no patients that discontinued the study due to adverse events.
Massart et al.[48] (2013) GH vs placebo	MA Patients with SHOX-D treated with GH	N=66 24 months	Primary: Final linear height and bone age Secondary: Not reported	Primary: In patients affected by SHOX-D, the mean midparental height was in the normal range following treatment with GH (SDS, -1.594; 95% CI, -2.486 to -0.703), compared to the subnormal mean height at baseline (SDS, -3.083; 95% CI, -3.243 to -2.923). Height outcomes progressively tended to normalize during GH treatment, although the major catch-up growth was detected after 12 months (SDS, -2.731; 95% CI, -2.998 to -2.463). GH-induced growth was constant until final height was achieved, which was in the normal range (SDS, -2.263; 95% CI, -3.214 to -1.312). The bone age chronologically progressed during GH treatment in both SHOX-D patients. Secondary: Not reported
Growth Failure Associated With Turner Syndrome				
Takano et al. (abstract)[49] (1989) GH 0.5 IU/kg/week SC daily	MC, RCT Patients with TS	N=203 1 year	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported All three treatment groups showed significant growth increases. Fifty

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs GH 1 IU/kg/week SC daily vs GH 0.5 IU/kg/week SC daily plus anabolic steroid				percent of patients receiving 0.5 IU/kg/week and 80% of those receiving 1 IU/kg/week showed growth rates more than two cm per year greater than pretreatment values or beyond the second SD of the untreated growth rate. Plasma somatomedin C levels were elevated and no remarkable advances in bone age were observed during treatment. Antibody against GH was observed in 71.4 and 10.8% of the methionyl-humanized GH and methionine-free-humanized GH. However, the antibodies did not suppress the growth promoting effect of methionyl-humanized GH. No other significant changes in physical or laboratory examinations were observed. No glucose tolerance was observed.
Takano et al.[50] (1989) GH 0.5 IU/kg/week SC daily vs GH 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=80 1 year	Primary: Growth rate, bone age, laboratory parameters Secondary: Not reported	Primary: The growth rate significantly increased during treatment in most patients. Growth rates among patients with 45, X karyotype and patients with other chromosomal variants did not differ significantly in both treatment groups (P value not significant). During one year of treatment, the mean height increased up to 6.0±1.1 and 7.2±1.3 cm/year (from 3.7±1.0 cm/year) with 0.5 and 1 IU/kg/week, respectively (P<0.05 for both). Treatment with 0.5 IU/kg/week resulted in an increase in bone age between 0 and 2.2 with a mean of 0.9±0.6 years. Treatment with 1 IU/kg/week resulted in an increase in bone age between 0 and 1.9 with a mean of 0.8±0.6 years. The increases between the two doses were similar. Antibodies to GH were observed in 10 patients during treatment. The antibodies did not suppress the growth effect of GH. The plasma somatomedin C concentration increased during treatment and was greater with 1 IU/kg/week at two and four months. Neither the basal nor maximal concentration of glucose or insulin glucose relationship changed with 0.5 IU/kg/week. Treatment with 1 IU/kg/week increased basal glucose and basal and maximum concentration insulin significantly after treatment (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Takano et al.[51] (1989) GH (somatropin) 0.5 IU/kg/week SC daily vs GH (somatropin) 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=94 2 years	Primary: Growth rate, bone age, development of antibodies, laboratory parameters Secondary: Not reported	Primary: The growth rate of patients with 45, X karyotype and patients with other chromosomal variants did not differ significantly between the two treatments (data not reported). The growth rate significantly increased during treatment in most patients in various age groups. For patients less than eight years, only treatment with 1 IU/kg/week significantly increased the growth rate after one year (from 4.1±0.9 to 6.8±0.6 cm/year; P<0.001). For patients eight to 10 years of age, treatment with 0.5 IU/kg/week significantly increased growth rate after one year (from 3.8±0.4 to 5.9±1.1 cm/year; P<0.001), while 1 IU/kg/week did after one (from 3.6±0.6 to 6.8±1.7 cm/year; P<0.001) and two years (5.1±0.8 cm/year; P<0.001). For patients 10 to 12 years of age, treatment with 0.5 and 1 IU/kg/week significantly increased growth rates after one (from 3.9±0.9 to 5.8±1.1 and from 3.7±0.8 to 6.8±0.9 cm/year; P<0.001 for both) and two years (4.6±0.9 and 4.7±1.1; P<0.05 for both). For patients 12 to 14 years of age, treatment with 0.5 IU/kg/week significantly increased growth rate after one year (from 3.4±0.9 to 4.6±1.1 cm/year; P<0.001), while 1 IU/kg/week did after one (3.2±1.1 to 5.9±1.3 cm/year; P<0.001) and two years (4.2±0.9; P<0.05). For patients 14 years or older, only 0.5 IU/kg/week significantly increased growth rate after one year (from 2.4±0.6 to 3.5±0.6 cm/year; P<0.05). Overall, the growth rate increased significantly from 3.7±1.0 to 5.2±1.3 (P<0.001) after one year and to 4.1±1.1 (P<0.05) after two years with 0.5 IU/kg/week. Corresponding rates with 1 IU/kg/week were 3.5±0.9 to 6.3±1.4 (P<0.001) and 4.6±1.1 cm/year (P<0.001). The latter two rates were significantly greater compared to 0.5 IU/kg/week (P<0.001 and P<0.05, respectively). The growth rate was the greatest during the first and second six months of treatment and gradually declined. Bone age increased 1.6±0.9 and 1.9±1.0 years, respectively, with 0.5 and 1 IU/kg/week (P value not significant). Antibodies were observed in 18 patients. The antibodies did not suppress

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the growth effect of treatment. Somatomedin C concentrations increased during treatment and values were greater at two, six, eight and 12 months with 1 IU/kg/week compared to 0.5 IU/kg/week (P values not reported). Neither basal nor the maximum glucose concentration changed with either dose. Basal and maximum insulin increased significantly. HbA1c did not change significantly after one or two years. No patients developed glucose intolerance and there was no significant change in blood count, urinalyses or routine chemistry. Secondary: Not reported
Takano et al.[52] (1993) GH 0.5 IU/kg/week SC daily vs GH 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=161 3 years	Primary: Height velocity, height velocity SDS, height SDS, treatment effectiveness, safety Secondary: Not reported	Primary: During the first, second and third year of treatment with 0.5 IU/kg/week, the mean height velocity was 6.0±1.3, 4.6±1.0 and 4.0±1.3 cm/year, respectively. The corresponding values with 1 IU/kg/week were 6.9±1.3, 5.0±1.2 and 4.3±1.1 cm/year, respectively. Values observed during the three years were always greater compared to pretreatment. Only during the first and second years did the 1 IU/kg/week dose significantly increase height velocity to a significant extent (P<0.05 for both). Before and during the first, second and third year of treatment with 0.5 IU/kg/week, the mean height velocity SDS was -0.24±0.99, 2.70±1.39, 1.23±1.06 and 0.89±1.34, respectively. The corresponding values with 1 IU/kg/week were -0.24±0.93, 3.57±1.36, 1.72±1.20 and 1.25±1.14, respectively. Values observed during the three years were always greater compared to pretreatment. Again, 1 IU/kg/week increased height velocity SDS by a significant extent during only the first and second year (P<0.05 for both). There were no correlations between the increase in height velocity in three years and the chronological age, bone age, height and IGF-1 values before treatment; however, there was a significant reverse correlation with the pretreatment growth rate (P<0.001). The mean total increases in height SDS were 1.00±0.61 and 1.32±0.58 with 0.5 and 1 IU/kg/week, respectively (P<0.01). During the three years, secondary sexual characteristics appeared incompletely in 17 and 11 patients receiving 0.5 and 1 IU/kg/week, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Efficacy, evaluated as the increased height velocity as expressed by the change in SDS for chronological age, was observed in 82.4, 67.6 and 48.6% of patients receiving 0.5 IU/kg/week during the first, second and third year. The corresponding proportions with 1 IU/kg/week were 94.6, 76.2 and 62.4%. The effectiveness of GH was also calculated as the height SDS at six years minus the baseline height SDS, and treatment was tentatively considered as being effective if the change >1. Therefore, treatment was effective in 50.0 and 75.3% of patients receiving 0.5 and 1 IU/kg/week (P<0.01). After three years, some patients already exceeded their projected adult height. Adverse events were uncommon. Glucose intolerance did not occur in any patient, though basal and maximal insulin levels after glucose administration increased slightly. Bone age did not advance beyond the changes in chronological age. At the end of three years, antibody was observed in three of 161 patients. Secondary: Not reported
Takano et al.[53] (1995) GH 0.5 IU/kg/week SC daily vs GH 1.0 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=63 6 years	Primary: Height velocity, degree of overweight, treatment effectiveness Secondary: Not reported	Primary: The height velocity was greatest during the first year of treatment, with height velocity increasing from 4.0±1.0 to 6.0±1.2 cm/year with 0.5 IU/kg/week and from 3.6±1.0 to 7.0±1.4 cm/year with 1 IU/kg/week. Only during the first two years of treatment did 1 IU/kg/week result in a significantly larger height velocity compared to 0.5 IU/kg/week (P value not reported). Patients with GHD did not differ from those without GHD. There was no correlation between the yearly growth rate increases for six years and the chronological age, bone age or height of patients. However, there was a significant negative correlation with the pretreatment growth rate. The mean degree of overweight calculated for 0.5 IU/kg/week increased significantly from 14.0±18.0 to 25.1±18.0% after six years (P<0.05) and for 1 IU/kg/week from 12.7±15.4 to 19.2±13.1% (P<0.05). There was no difference in the increase in overweight between the two treatments (P value not reported). After six years, secondary sex characteristics appeared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				incompletely in 20 of 63 patients and occurred in similar incidences with the two treatments. The effectiveness of GH was calculated as the height SDS at six years minus the baseline height SDS, and treatment was tentatively considered as being effective if the change was >1. Therefore, treatment was effective in 58 and 87% of patients receiving 0.5 and 1 IU/kg/week. After six years, patients tended to exceed their projected adult height. Secondary: Not reported
Bertrand et al.[54] (1996) GH 0.45 IU/kg/week SC daily for 1 year, followed by GH 0.90 IU/kg/week SC daily for 2 years (G1) vs GH 0.90 IU/kg/week SC daily for 2 years (G2) Estrogen was permitted in patients with a bone age >12 years.	MC, PG, RCT Female pediatric patients with TS, height 1.5 SD or more below the mean for chronological age, height velocity below the mean age for bone age and weight between -2 and 3 SD of weight for height	N=97 3 years	Primary: Compliance, growth response, adverse events Secondary: Not reported	Primary: Nine patients discontinued GH over the three years due either to poor compliance with study visits, to inefficiency of treatment, to family choice, to adverse events or as required by protocol amendment. Compliance with treatment was usually good. Significant differences in mean height velocity between the two doses were observed only for the first year (5.5 vs 6.7 cm/year; P=0.0001). Mean height velocity was markedly accelerated in both treatment groups after six months and during the first year. Doubling the GH dose at month 12, significantly increased height velocity (P=0.02). Although progressive attenuation of the effect with time was observed, height velocity remained above the mean for reference untreated TS patients during the three years in both treatment groups. Responders to treatment were 45 vs 70% for G1 and G2 (P=0.014). A significant difference between G1 and G2 was observed in mean height gain after one (P<0.0001) and two years (P=0.0061). After three years, the mean height gain was 1.06±0.06 and 1.17±0.05, but the difference was no longer significant (P value not reported). Bone maturation did not differ at any time between the two treatments over the 36 months (33.7 vs 31.9 months; P value not reported). Weight was stable within G2 and increased significantly within G1, although there was no difference between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean IGF-1 increased in both treatment groups for the first three months (from 1.02 to 1.22 within G1 and from 1.00 to 1.55 within G2). Over the first year, the increment was significantly higher within G2 (P value not reported). The more frequent adverse events were application site disorders, resistance mechanism disorders, general disorders, gastrointestinal disorders and skin and appendage disorders. Twenty eight hospitalizations for surgery, seemingly unrelated to GH, were classified as severe adverse events. Mean plasma fasting glucose and HbA1c remained stable. Mean free T_4 decreased slightly, but not significantly, over the three years without clinical effects. Secondary: Not reported
van Teunenbroek et al.[55] (1996) GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6	MC, RCT Female patients 2 to 11 years of age with TS who are treatment naïve, height below the 50th percentile and normal thyroid function	N=68 4 years	Primary: Growth response, bone maturation, final height prediction, GH measurements, GHBP, IGF-1 and IGFBP-3 Secondary: Not reported	Primary: Compared to baseline, mean height velocity increased significantly with all three treatments from approximately six to 10 cm/year during the first year of GH. Thereafter, a waning of the growth response was observed. In the second year, mean height velocity in Groups B and C were significantly higher compared to Group A. With a dose of 8 IU/m^2/day in Group C, mean height velocity was significantly higher compared to Group B. In the fourth year, only in Group C the mean height velocity remained significantly higher compared to Group A. During the first year of treatment, 29% of all patients managed to double their height velocity. Height velocity SDS for chronological age in Groups B and C were significantly higher compared to Group A in the second through fourth year of treatment. However, in the third and fourth year, Group C was not different than Group B. The change in height SDS for chronological age from the first year was significantly higher for the combined Groups B and C compared to Group A (P<0.0001). The second dose-increment in the third year, as well as in the combined third and fourth year, resulted in a significantly higher change from year two in height SDS for chronological age for Group C compared to Group B (P=0.04 and P=0.02). The increase in mean height

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IU/m^2/day SC for 1 year, followed by 8 IU/m^2/day SC for 2 years (Group C)				SDS for chronological age was highest in the first year of treatment (>1 SDS), without a difference between treatment groups. The change in RUS bone age over the change in chronological age was not different between treatment Groups over the four years, nor during any individual year of treatment. For all groups, the highest advance was found during the third year and the lowest during the fourth year of GH (data not reported). Mean final height prediction increased significantly for all treatment groups after four years (P values not reported). Differences between treatment groups for the four year change were not observed, though mean values in Groups B and C were higher than those in Group A. There was a significant dose-dependent increase of the maximum GH level and area under the curve. In contrast, the time to peak concentration, clearance and elimination half-life were not difference between the three doses of GH. GHBP levels after six months of treatment did not differ from baseline. Within treatment groups, each point in time was significantly higher than the previous, except for 30 months (all treatment groups) and 42 months (Group B). At 30 months, IGF-1 levels for Groups B and C became significantly higher compared to Group A (P<0.004), but at 48 months only Group C was still significantly higher than Group A (P=0.008). Mean IGFBP-3 levels only increased significantly after six months of treatment (P<0.0001). At the end of the trial, 31 and 35% of all patients had IGF-1and IGFBP-3 levels higher than the 95th percentile for healthy individuals at the pubertal peak. There were no differences between treatment groups. The IGF-1:IGFBP-3 showed an increase over time, but there were no differences between treatment groups. Secondary: Not reported
Sas et al.[56] (1999)	ES of van Teunenbroek et al.[51]	N=68	Primary: Growth response,	Primary: After seven years, 55 of 65 patients (85%) had a height within the normal

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 1 year, followed by 8 IU/m^2/day SC for 2 years (Group C)	Female patients 2 to 11 years of age with TS who are treatment naïve, height below the 50th percentile and normal thyroid function	7 years	bone maturation Secondary: Not reported	range for healthy individuals, whereas only 10 patients (15%) had a height just below the 3rd percentile. In all three treatment groups, height SDS increased significantly (P<0.001). The mean change in SDS score was significantly higher in Groups B and C compared to Group A (95% CI, 0.08 to 0.95; P=0.02 and 95% CI, 0.38 to 1.27; P=0.001, respectively). The differences between Groups B and C were not significant (95% CI, -0.19 to 0.81; P=0.22). After seven years, the mean height SDS in all three treatment groups had increased to values within the normal range for healthy individuals. Data indicates that treatment with GH was associated with an acceleration of bone maturation compared to healthy individuals. No differences in bone maturation were observed between treatment groups. Secondary: Not reported
van Pareren et al.[57] (2003) GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B)	Post hoc analysis of van Teunenbroek et al.[51] Female patients 2 to 11 years of age with TSs who are treatment naïve, height below the 50th percentile and normal thyroid function	N=68 7 years	Primary: Final height, estrogen effect Secondary: Not reported	Primary: Final height was 157±6.5, 162.9±6.1 and 163.6±6.0 cm in Groups A, B and C. When translated to SDS, using references for healthy individuals, final height was -1.6±1.0, -0.7±1.0 and -0.6±1.0 cm in Groups A, B and C. The difference in final height, corrected for height SDS and age at the start of treatment, was significant between Groups A and B (regression coefficient, 4.1; 95% CI, 1.4 to 6.9; P<0.01) and between Groups A and C (5.0; 95% CI, 2.3 to 7.7; P<0.001), but not between Groups B and C (0.9; 95% CI, -1.8 to 3.6; P value not reported). Fifty of 60 patients (83%) had reached a normal final height. The mean gain in final height in Group A was 11.9±3.6 cm, being significantly lower compared to 15.7±3.5 cm in Group B (4.2; 95% CI, 1.5 to 6.9; P<0.01) and compared to 16.9±5.2 cm in Group C (5.2; 95% CI, 2.6 to 7.8; P<0.001), but the height gain in Group B was not different from that in Group C (1.0; 95% CI, -1.6 to 3.6; P=0.44). Similarly, the mean increase in SDS from start of treatment until

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 1 year, followed by 8 IU/m^2/day SC for 2 years (Group C) In the first 4 years of treatment, no estrogen for pubertal induction was given to patients. After four years, estrogen treatment was started at the yearly visits after the patient had reached the age of 12. In patients who become 12 years old during the first 4 years of treatment, estrogen treatment was started at 4 years of treatment. If puberty had developed spontaneously before the start of estrogen therapy, no exogenous estrogen				final height in Groups B and C was significantly higher compared to Group A (0.7; 95% CI, 0.31 to 1.11; P<0.001), but the increase in Group B was comparable to Group C (0.12; 95% CI, -0.27 to 0.5; P=0.5). Height velocity in the year after initiation of estrogen treatment compared to the height velocity in the previous year showed no difference. The downward trend in height velocity before initiation of estrogen treatment; however, changed significantly to a stable height velocity after initiation (P<0.05). Bone maturation in the year before and in the year after initiation of estrogen treatment was no different. GH dosage, GH duration before start of estrogen and height at puberty had no significant effect on the differences of height velocity, in the change in height velocity, or in bone maturation. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
was given.				
Massa et al.[58] (1995) GH (Humatrope®) 8 IU/m^2 SC TIW in patients <12 years of age vs GH (Humatrope®) 8 IU/m^2 SC TIW in patients >12 years of age vs GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients <12 years of age vs GH (Humatrope®) 4.0 IU/m^2 SC 6 times a week in patients >12 years of age Estrogen therapy was initiated when patients reached 12 years of age and to patients >12 years of age when they	RCT Pediatric patients with TS	N=45 Not reported	Primary: Final height Secondary: Not reported	Primary: Treatment with GH resulted in a significantly greater final height compared to reference treatment naïve patients with TS (152.3±5.3 vs 147.0±6.3 cm; P<0.001). No differences were observed between patients <12 years of age and those >12 years of age (151.1±4.3 vs 152±5.6 cm; P value not reported) or between three and six times weekly dosing (151.8±5.6 vs 152.8±4.8 cm; P value not reported). For all patients, the difference between final height and the initial predicted adult height (147.6±5.4 cm) was 4.7±3.8 cm (P<0.0001). Final height was significantly related to height (P<0.005) and height SDS (P<0.001) at baseline, but not to chronological or bone ages (P values not reported). The difference between final height and initial predicted adult height; however, was related to chronological age (P<0.005) but not to the other variables. In contrast, the difference between final height and projected adult height from initial height SDS was inversely related to the initial height (P<0.05), height SDS (P<0.01) and bone age (P<0.005) but not to chronological age (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enrolled. After 2 years, GH was changed to 6 IU/m^2 SC 6 times a week in patients >12 years of age.				
Nienhuis et al.[59] (1993) GH (Humatrope®) 8 IU/m^2 SC TIW in patients <12 years of age (A1) vs GH (Humatrope®) 8 IU/m^2 SC TIW in patients >12 years of age (B1) vs GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients <12 years of age (A2) vs GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients >12 years of age (B2) Estrogen therapy	RCT Pediatric patients with TS	N=29 4 years	Primary: Height velocity, height, bone age, predicted adult height, final height Secondary: Not reported	Primary: There was an increase in height velocity, which was greatest in the first year and still significant in the second year of therapy, and there was also a significant difference between three and six times weekly dosing (P values not reported). In groups A1 (P=0.15 and P=0.20) and A2 (P=0.17 and P=0.96) in the third and fourth years, height velocity was no longer significantly greater than baseline, nor was there a significant difference between three and six times weekly dosing (P value not reported). In patients >12 years of age, Group B, height velocity was only significantly greater than before therapy in the first year. In Group B1, height velocity SDS increased after the dose and frequency were increased. In Group B2, no further decrease in height velocity SDS was observed. In patients <12 and >12 years of age, height increased from 120.8 to 143.4 cm and from 136.0 to 152.7 cm. The total increment in height SDS in Groups A1, A2, and B was 1.3, 1.7 and 1.1, respectively, and was significant for all (P<0.01). There was no difference between Groups A1 and A2 (P=0.12), nor between Groups B and A (P=0.07). Chronological and bone ages at baseline correlated negatively with the increment in height SDS (P=0.006 and P=0.01), respectively. While the increment in height SDS did not differ between Groups A1 and A2, the height SDS after four years was significantly greater with Group A2 (P=0.05). For bone age, the observed bone age advancement was compared to the expected bone maturation of reference patients. In Group A1 and B, there was no difference between the observed and expected skeletal maturation (P values not reported). In Group A2, the observed bone maturation of 4.0 years was significantly greater than the expected 3.2 years (P=0.004). The predicted adult height increased significantly in Groups A2 and B

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
was initiated when patients reached 12 years of age and to patients >12 years of age when they enrolled. After 2 years, GH was changed to 6 IU/m^2 SC 6 times a week in patients in Group B1.				(P=0.001), but not in Group A1 (P=0.11). The predicted adult height after four years was not significantly different between three and six times a week dosing (P=0.63), but the mean increment in Group A2 was significantly higher compared to Group A1 (P=0.02). In Group B, the mean attained height after four years was 5.8 cm greater than the initial prediction (P value not reported). The increment in height prediction was significantly greater in Group A (P=0.03). Final height data is presented for a total of 23 patients. For this group the mean initial age was 15.5 years and duration of therapy 2.9 years. There was a significant increment in height SDS, of 0.5 SDS during treatment (P=0.001). At the end of therapy, the mean final height was 150.4 cm and the SDS for age was 1.1. There was no difference in increment of predicted adult heath between three and six times weekly dosing (P=0.34). Secondary: Not reported
Baxter et al.[60] (2007) GH (somatropin) for ≥6 months vs placebo or no treatment	SR (4 RCTs) Pediatric patients with TS	N=365 1 year	Primary: Final height, height SDS and growth velocity Secondary: Bone age, psychological outcomes, adverse events	Primary: One trial reported final height data. Patients achieved a final height of 148±6 and 141±5 cm with GH and no treatment (95% CI, 6 to 8). These patients also had a change in height SDS of 1.6±0.6 and 0.3±0.4 (MD, 1.3; 95% CI, 1.1 to 1.5). One trial reported height SDS data. Height SDS was 1.2 (95% CI, 1.0 to 1.5) greater in patients receiving GH compared to patients receiving no treatment. Three trials reported growth velocity data. Two trials reported growth velocity after one year of treatment and patients who received GH grew approximately three cm more in the year than those who did not receive treatment (MD, 3 cm/year; 95% CI, 2 to 4). One of these trials reported growth velocity after two years of treatment that was two cm per year greater with treatment (95% CI, 1.3 to 2.3). The third trial reported growth velocity after 18 months of treatment and patients who received GH grew three cm per year more compared to those who did not receive treatment (95% CI, 2 to 3). Two trials reported that growth velocity SDS for the first year of treatment with GH was approximately three SD greater than no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment (MD, 3.2; 95% CI, 2.8 to 3.6). One of these trials reported growth velocity SDS after two years and reported it was 1.6 SD greater (95% CI, 1.1 to 2.2) with GH compared to no treatment. Secondary: One trial reported the ratio of changes in bone age to changes in chronological age. After one year of treatment the difference in the ratio was 0.2 (95% CI, -0.03 to 0.40). After two years of treatment the difference in the ratio was -0.1 (95% CI, -0.5 to 0.3). One trial reported on psychological outcomes in relation to GH treatment, but the selective reporting of results leaves in doubt the nature of the unreported results. Bearing in mind possible biases, the presented results suggest the possibility that patients treated with GH do have better psychological adjustment than patients receiving no treatment. Reporting of adverse events was minimal. In one trial, acute otitis media occurred or worsened in 29 and 13% of patients receiving GH and placebo, respectively. In one trial, there were significant differences in treatment emergent adverse effects between treated and control groups.
Quigly et al.[61] (2021) Somatropin (Humatrope®)	Observational ES of MC, OL, PG, RCT Patients aged nine months to four years with karyotype-proven Turner syndrome, normal baseline urinalysis, hemoglobin, and thyroid stimulating hormone; and adequate thyroid hormone replacement for those with hypothyroidism	N=69 10 years	Primary: Compared height SDS at near adult height (defined as the first height measurement obtained after height velocity was ≤2.0 cm/year or bone age ≥14.5 years) of girls who received two years of GH in the MC, OL, PG, RCT study (early-treated group) vs those who were untreated during that period	Primary: The primary efficacy analysis did not demonstrate a significant height SDS difference at near adult height for the early-treated group vs the early-untreated group. Secondary: The early-treated group was taller than the early-untreated group at all time points from preschool to maturity and was significantly taller at the onset of puberty (P=0.016), however, the difference was not significant at near adult height.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(early-untreated group) Secondary: Compared height at near adult height (defined as the first height measurement obtained after height velocity was ≤2.0 cm/year or bone age ≥14.5 years) of girls who received two years of GH in the MC, OL, PG, RCT study (early-treated group) vs those who were untreated during that period (early-untreated group)	
Growth Failure In Children Born Small For Gestational Age				
Jung et al.[62] (2014) OPTIMA GH (Humatrope®) 0.067 mg/kg/day (fixed high dose) vs GH (Humatrope®) 0.035 mg/kg/day individually adjusted (IA dose) after 3	Post-hoc analysis of OL, RCT Patients ≥3 years of age born SGA, had short stature (height SDS ≤-3), were still prepubertal, and had bone age of nine years or less (females) or ten years or less (males)	N=169 1 year	Primary: Mean height SDS and height velocity changes, observed versus predicted response Secondary: Not reported	Primary: In the IA-dose group, 42 children were considered good responders based on the predicted height SDS gain (≥0.75) at three months and remained on the initial dose, while 38 were considered poor responders and had a dose increase following the growth prediction at three months. During the first three months, when both IA groups received the same GH dose, the mean gain in height velocity was 8.8 centimeters per year (95% CI, 8.1 to 9.5) for the patients who required a dose increase compared with 12.3 centimeters per year (95% CI, 10. to, 13.7) for the IA low dose group. When the dose was increased from three months onwards for the IA high dose group, the catch-up in height velocity continued such that height velocity did not start to decrease and the mean change from baseline to 12 months was similar for both groups. Least squares mean difference for IA low dose versus IA high dose for height velocity at 12 months was -0.07

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
months, which remained unchanged if predicted 12-month change in height SDS was ≥0.75 or was increased to 0.067 mg/kg/day if predicted 12-month change in height SDS was <0.75				centimeters per year (95% CI, -0.74 to 0.60; P=0.836). Mean difference between the IA low dose and IA high dose groups for height SDS gain at 12 months was 0.03 (95% CI, –0.13 to 0.18; P=0.714). Eleven out of 21 patients reached a 12 month height SDS gain of ≥0.75. In individually adjusted poor responders, increasing GH dose at three months maintained mean height velocity, with 72.7% reaching a 12-month height SDS gain of ≥0.75 vs 73.8% in individually adjusted dose GH good responders, who continued on low GH dose. For patients on the fixed high dose, a height SDS gain of ≥0.75 was achieved by a majority with a predicted good response (94.1%) but by only half of those with a predicted poor response (52.4%). Secondary: Not reported
Jensen et al.[63] (2014) NESGAS GH 0.067 mg/kg/day vs GH 0.025 mg/kg/day vs IGF-1 titration All subjects were treated with one year of high-dose GH (0.067 mg/kg/day) prior to randomization	MC, PG, RCT Pre-pubertal patients born SGA	N=92 2 years	Primary: Height gain Secondary: IGF-1 levels, changes in bone age	Primary: The high-dose GH therapy for two years resulted in greater height gain (ANOVA P<0.0001) and weight gain (ANOVA P=0.002) during the last year of the trial compared with both the low-dose and IGF-1 titration groups. In the IGF1 titration group there was a trend towards a lower growth response (0.15; SD 0.16) during the last year of the trial when compared with the low-dose group (0.24; SD. 0.18), although this was not significant (P=0.17). Secondary: The IGF-1 titration group had lower IGF-1 levels (1.16) after two years of the trial compared to the low-dose and the high-dose groups (1.76 and 2.97, respectively). There were no significant differences among the low-dose, high-dose or IGF1 titration groups for changes either in bone age during the two years of the trial (ANOVA P=0.38) or bone age corrected for chronological age after two years of treatment (ANOVA P=0.27).
Lundberg et al.[64]	MC, RCT	N=104	Primary	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2015) GH 0.067 mg/kg/day once daily vs GH 0.067 mg/kg/day divided twice daily vs GH 0.033 mg/kg/day	Patients at the onset of puberty who had received GH 0.033 mg/kg/day during at least one prepubertal year	Followed from GH start to adult height	Change and obtained mean on-treatment IGF-1, IGFBP3, and IGF-1/IGFBP3 rations during prepuberty and puberty Secondary: Not reported	Mean prepubertal increases one year after GH start with 2.1 IGF-1, 0.6 IGFBP3, and 1.5 IGF-1/IGFBP3 ratio. A significant positive correlation was found between prepubertal change in IGFs and both prepubertal and total gain in height (SDS). Mean pubertal level of IGF-1 (SDS) was higher in GH 0.067 mg/kg/day dosing versus GH 0.033 mg/kg/day dosing (P=0.031). First year pubertal change in IGF-1 (SDS) was significantly higher in the GH 0.067 mg/kg/day dosing groups versus GH 0.033 mg/kg/day group (0.5 vs -0.1, respectively, P=0.007), as well as change in IGF-1 (SDS) to the pubertal mean level (0.2 vs -0.2; P=0.028). Secondary: Not reported
van der Steen et al.[65] (2015) GH (Genotropin®) 2 mg/m^2 daily (~0.067 mg/kg/day) vs GH (Genotropin®) 1 mg/m^2 daily With or without combination with two years of GnRH analog	RCT Prepubertal patients ≥8 years of age with SGA and well-documented growth data from birth to start of treatment	N=107 Treated until adult height (average treatment duration was 5.9 years)	Primary: Body composition, blood pressure, lipid profile Secondary: Not Reported	Primary: At adult height, fat mass percentage SDS, lean body mass SDS, blood pressure SDS, and lipid profile were similar between children treated with combined GH/GnRH analog and those with only GH. In the pubertal subgroup, fat mass percentage SDS was lower during treatment with GH 2 mg/m^2 per day. There was no GH dose-dependent effect on lean body mass SDS, blood pressure, and lipid profile. Secondary: Not reported
De Schepper et al.[66] (2016) GH (Genotropin®) 0.035 mg/kg/day vs	MC, OL, RCT Patients 19 to 29 months of age diagnosed with SGA at birth	N=43 2 years	Primary: Height SDS Secondary: Mental and psychomotor development, growth velocity,	Primary: Change from baseline in height SDS was significantly greater in GH treatment versus the control group at month 12 (1.03 versus 0.14) and month 24 (1.63 versus 0.43) (P<0.001 for both). Secondary: Baseline and follow-up Mental Development Index and Psychomotor Development Index values were similar between the two groups. Mental

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
no GH			body weight, body mass index, head growth, bone age, safety	Development Index mean difference from baseline was 2.43 (P=0.738) and Psychomotor Development Index mean difference from baseline was -4.51 (P=0.301). Growth velocity SDS was significantly higher in the GH treatment group compared with the control group at 12 months (P<0.001), but not at 24 months. Changes from baseline in height, head circumference SDS and BMI were assessed by descriptive statistics; no mean differences or P-values were reported. Mean change (SD) from baseline to 24 months in bone age was greater in the GH compared to the control group (21.20 (7.28) and 18.78 (8.18) months, respectively). A greater number of all-causality, treatment-emergent adverse events were reported in the GH group (119 events in 21 patients) versus the control group (52 events in 19 patients. The most commonly reported AE was infection and infestation, occurring in 95.2% and 68.2% of patients in the GH and control groups, respectively. The most common treatment-related TEAE was adenoidal hypertrophy, reported in two patients in the GH group.
Kappelgaard et al.[67] (2014) GH 0.033 mg/kg/day vs GH 0.067 mg/kg/day	DB, PG, RCT Patients 3 to 8 years of age born SGA	N=65 260 weeks	Primary: Changes in metabolic parameters (glucose, insulin, TC, LDLc, HDLc), weight change, BMI SDS, vital signs Secondary: Not reported	Primary: A positive correlation between change in height SDS and change in IGF-1 SDS were observed. Insulin and glucose levels were mostly unaffected. Favorable changes in lipid profiles were maintained for the study duration. No negative changes in weight, BMI SDS, or vital signs were noted. Secondary: Not reported
De Schepper et al.[68] (2008) GH (Genotonorm®)	RCT Patients 3 to 8 years of age SGA with	N=25 2 years	Primary: Growth, body composition, safety	Primary: Patients receiving GH gained more height and weight compared to the control group. GH was associated with a marked reduction (P<0.001) in limb skinfolds but not truncal skinfolds.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
66±3 µg/kg/day SC vs no GH (control)	birth weight, length or both below -2 SD for gestational age; current height below -2.5 SD; height velocity below 1 SD		Secondary: Not reported	GH was accompanied by a gain of lean mass (P<0.0001) and by a centripetal redistribution of fat mass (P<0.0001), but not by an overall gain or less of fat mass. All patients remained prepubertal, and none had a noteworthy adverse event during the two years. Secondary: Not reported
Arends et al.[69] (2003) GH (Norditropin®) 33 µg/kg/day SC vs no GH (control) 12 additional patients with GHD were also treated with GH (Norditropin®) 33 µg/kg/day SC. In order to evaluate the GH-induced effect on growth in relation to the severity of growth retardation at start, results of the present trial were compared to those of patients receiving GH 66	MC, OL, RCT Patients with a chronological age 3.00 to 7.99 years with short stature born SGA; non-GHD; birth length SDS below -2 SDS for gestational age; an uncomplicated neonatal period; height SDS for age below -2; height velocity SDS for age below zero; prepubertal and normal liver, kidney and thyroid functions	N=104 3 years	Primary: Growth, growth factors, bone age, BMD, safety Secondary: Not reported	Primary: Height SDS increased significantly from -3.0 to -1.3 SDS after three years with GH (P<0.001). Patients with GHD demonstrated similar growth, as height increased significantly from -3.4 to -1.2 SDS after three years (P<0.001). Control; however, demonstrated a small increase in height SDS from -3.2 to -2.9 SDS (P<0.001). IGF-1 and IGFBP-3 increased significantly in all patients receiving GH after three years. In the total group, the three year change in both IGF-1 and IGFBP-3 SDS correlated significantly with the three year change in height SDS (P<0.001 for both). For all patients receiving GH, this correlation was weaker but still significant (P=0.02). During the three years, the delay in bone maturation of control remained unchanged. In contrast, all patients receiving GH demonstrated a significant increase in bone maturation. The highest ratio between the change in bone age and the change in chronological age with GH was observed during the second year of treatment, and for patients with GHD during the first year of treatment with GH. During the third year, this ratio was comparable for all three treatments. During the entire three year period, the mean ratio was 4.3/3.0 yr/yr with GH and 3.2/3.0 year/year with control (P<0.001). No difference was observed in mean total body, lumbar spine and apparent density BMD SDS at baseline and during GH treatment between patients treated with GH and those with GHD (data not reported). Therefore, BMD for these two groups were presented together. After two and three years of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day SC in another trial.				treatment, all patients had a total body, lumbar spine and apparent density BMD SDS in the normal range. GH was well tolerated and no adverse events were reported during treatment that could be attributed to treatment. Thyroid function and HbA1c levels remained normal during the trial. Secondary: Not reported
Maiorana et al.[70] (2009) GH 33 or 67 µg/kg/day vs no treatment	MA (4 MC, RCTs) Prepubertal pediatric patients who had a birth weight and/or length of <-2 SDS and who had never received GH treatment	N=391 Mean duration 7.30±0.35 years (treatment was discontinued once adult height was reached)	Primary: Adult height SDS, change in height SDS Secondary: Adult height SDS and change in height SDS corrected for target height	Primary: Mean adult height SDS was -1.5 in the GH group and -2.4 in the untreated group, with a difference of 0.9 SDS or 5.7 cm (P<0.0001). There was no difference between the 33 and 67 µg/kg/day regimens. Mean increase in height with GH treatment was 1.5 SDS, or 9.5 cm, compared to 0.25 SDS, or 1.6 cm, with no treatment (P<0.0001). Secondary: The difference between the GH and untreated groups with regard to corrected adult height SDS was 0.78 (P<0.0001). Corrected gain in height SDS was 1.46 and 0.40 in the GH and untreated groups, respectively (P<0.0001).
Boguszewski et al.[71] (1998) Somatropin (Genotropin®) 0.1 IU/kg/day (low dose) vs somatropin (Genotropin®) 0.2 IU/kg/day (high dose)	OL, RCT SGA prepubertal pediatric patients 2 to 8 years of age at start of study, height SDS <-2, height velocity SDS <1, birth weight and/or length SDS <-2 for gestational age, gestational age > 30 weeks, serum GH >20 mU/L during	N=48 3 years	Primary: Growth response, safety Secondary: Not reported	Primary: After one year, the low dose and high dose treatment groups had significantly greater change in height SDS compared to the untreated group (P<0.001 for both). After two years, the low dose and high dose treatment groups had significantly greater change in height SDS compared to the untreated group (P<0.05 and P<0.01). At year three, there were no significant differences in the low dose or high dose treatment group in height SDS compared to baseline. After one year, the low dose and high dose treatment groups had significantly smaller attainted height SDS compared to the untreated group (P<0.05 and P<0.01). After two years, the low dose and high dose treatment groups had significantly smaller attainted height SDS compared to the untreated group (P<0.01 and P<0.001). At year thee, the attainted

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no treatment After completion of 24 months, patients could continue with treatment and the untreated patients could continue at a dose of 0.2 IU/kg/day	240 hour profile or after GH stimulation test			height SDS was significantly less in the low dose and high dose treatment groups compared to baseline (P<0.001 for both). After one year, the low dose and high dose treatment groups had a significantly smaller difference between height SDS and mid-parental height SDS compared to the untreated group (P<0.05 and P<0.001). After two years, the low dose and high dose treatment groups had significantly smaller difference between height SDS and mid-parental height SDS compared to the untreated group (P<0.01 and P<0.001). At year three, the difference between height SDS and mid-parental height SDS was significantly less in the low dose and high dose treatment groups compared to baseline (P<0.001 for both). There were no adverse events detected that were considered drug related. Secondary: Not reported
Chatelain et al.[72] (1994) GH 0.4 IU/kg/week (low-dose group) vs GH 1.2 IU/kg/week (high-dose group) vs placebo for 6 months followed by GH 0.4 or 1.2 IU/kg/week for 18 months	DB, MC, OL, PC, RCT Prepubertal pediatric patients between 4 and 11 years of age for boys or 4 and 10 years of age for girls who were diagnosed with IUGR	N=95 2 years (DB, PC for 6 months followed by OL for 18 months)	Primary: Height velocity, change in height SDS Secondary: Bone age, age at onset of puberty, change in serum IGF-1 levels, carbohydrate metabolism, free T_4 and safety	Primary: At six months, height velocity was greater in the high-dose group compared to the low-dose group (9.2±0.4 vs 6.8±0.3 cm/year; P<0.0005). Patients receiving GH had a higher height velocity SDS compared to those receiving placebo (5.0±0.3 cm/year; P<0.0025). At two years, height velocity remained higher in the high-dose group compared to the low-dose group (7.3±0.2 vs 6.2±0.2 cm/year; P=0.0003). At two years, the mean increase in height SDS over chronological age was greater with high-dose GH compared to low-dose GH (1.25±0.07 vs 0.66±0.07; P<0.0001). Secondary: There were no significant differences between the two groups with regard to bone age at two years, age at onset of puberty and serum IGF-1 levels. No significant changes were seen in fasting blood glucose, HbA1c and free T_4 during the study. The incidence of adverse events was similar between the two groups. Most commonly reported adverse events were local pain, erythema and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ecchymosis. One patient in the high-dose group was diagnosed with hypothalamic dysgerminoma during the study, and GH was discontinued.
Butenandt et al. (abstract)[73] (1997) GH 0.1 IU/kg/day vs GH 0.2 IU/kg/day vs no GH (control)	RCT Pediatric prepubertal patients with SGA and nonGHD	N=69 2 years	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported After two years, there was a significant increase in height velocity SDS with GH compared to control. Mean values after the first year were -1.2, 2.8 and 5.5 with control, GH 0.1 IU/kg/day and GH 0.2 IU/kg/day. Corresponding values during the second year of treatment were -0.9, 1.6 and 2.9. A significant difference between 0.1 and 0.2 IU/kg/day was observed during the first year, but there was no difference during the second year of treatment. Catch-up growth was achieved for 86 and 95% of patients receiving 0.1 and 0.2 IU/kg/day during the first year of treatment and was maintained in 65 and 79% of patients during the second year. GH was associated with a distinct acceleration of bone age. Tolerance was good. No clear trends were seen in any of the laboratory parameters.
Bannink et al.[74] (2010) Somatropin (Norditropin®) 33 µg/kg/day SC (low-dose group) vs somatropin (Norditropin®) 67 µg/kg/day SC (high-	DB, MC, PG, RCT Prepubertal pediatric patients between 3 and 11 years of age for boys or 3 and 9 years of age for girls who were diagnosed with SGA and who had a height <-2 SDS and height velocity ≤0 SDS	N=38 Mean duration 9.04 years (treatment was discontinued once adult height was reached)	Primary: Adult height SDS and change in health-related quality of life measured by EQ-5D score Secondary: Not reported	Primary: Adult height SDS was -1.8 in the low-dose group and -1.5 in the high-dose group (P value not reported). There was an improvement in adult height SDS by 1.4 and 1.7 SDS in the low- and high-dose groups, respectively (P=0.11). Change in EQ-5D score was 0.112 and 0.115 in the low- and high-dose groups, respectively (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose group)				
Sas et al.[75] (1999) GH (Norditropin®) 3 IU/m^2/day SC vs GH (Norditropin®) 6 IU/m^2/day SC	MC, RCT Patients 3 to 11 years of age with SGA and short stature, birth length SDs below -1.88 for gestational age, height SDS for chronological age below -1.88, height velocity SDS for chronological age of zero or less, without catch-up growth and an uncomplicated neonatal period	N=79 5 years	Primary: Height, bone age, BMI, IGF-1 and IGFBP-3, safety Secondary: Not reported	Primary: After five years, the mean height SDS for chronological age increased significantly from baseline with both doses (P<0.001 for both) and in conformity with the target height SDS. There was no difference between the two doses (2.2±0.6 vs 2.6±0.9; P=0.057). The mean ratio of the change in bone age to the change in chronological age per year was significantly higher than 1 for both doses (1.4±0.2 and 1.3±0.2, respectively; P<0.001). No differences in bone maturation were observed between the two doses (P value not reported). At baseline, mean bone age RUS was 0.6±1.0 year, whereas after five years it advanced to 1.0±1.1 year. After five years, height SDS for bone age increased significantly compared to baseline (P≤0.001). The increase was significantly greater with 6 IU/m^2/day (from -2.4±1.0 to 1.2±0.8) compared to 3 IU/m^2/day (from -2.1±1.1 to 1.5±0.8; P=0.004). In a subanalysis on prepubertal growth (n=23 and n=16), the increment in height SDS for chronological age was significantly increased with both doses (P<0.001). The increase was significantly greater with 6 IU/m^2/day (3.30±0.73 vs 2.35±0.51; P<0.001). The mean ratio of the change in bone age to the change in chronological age per year was significantly higher than 1 for both doses (1.39±1.17 and 1.37±0.22; P<0.001), without differences between the two (P value not reported). Height SDS for bone age increased significantly compared to baseline (P<0.05), and the increase was significantly greater with 6.0 IU/m^2/day (from -2.06±1.17 to -0.88±0.93 vs -1.86±1.11 to -1.49±0.89; P=0.02). The increase in predicted adult height after five years was 9.1±2.8 and 14.0±5.5 cm with 3 and 6 IU/m^2/day, being significantly increased compared to baseline with both doses (P<0.005) and significantly higher with 6 IU/m^2/day compared to 3 IU/m^2/day (P=0.02). After five years, BMI SDS was significantly increased to -0.3±1.2 and -0.2±0.8 with 3 and 6 IU/m^2/day (P<0.001 vs baseline), with no differences between the two doses.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				IGF-1 SDS was significantly higher than baseline at each visit for both doses. The IGF-1 SDS was significantly higher with 6 IU/m^2/day compared to 3 IU/m^2/day during the first three years. Thereafter, the difference was no longer significant. Results for IGFBP-3 were similar. The five year increase in height SDS for chronological age correlated negatively with baseline chronological age (P<0.001) and baseline bone age RUS (P<0.001). The change was not related to the target height SDS, baseline bone age delay, pretreatment height velocity SDS, baseline IGF-1 SDS, mean maximal plasma GH response during arginine tolerance test or characteristics of the 24 hour GH profiles established at baseline. No difference was also found between the patients with GHD and those with normal levels. Treatment was well tolerated and no adverse events were detected that were considered to be drug-related. With both doses, the mean fasting glucose level and area under the curve for glucose during oral glucose tolerance test did not significantly change during the first year of treatment compared to baseline. However, mean fasting insulin levels increased significantly with both doses after one year (P<0.001). In addition, the area under the curve for insulin during oral glucose tolerance test was significantly higher after one year of treatment (P<0.001). HbA1c remained in the normal range and no patent develop diabetes. Secondary: Not reported
Jung et al.[76] (2009) OPTIMA Somatropin (Humatrope®) 0.067 mg/kg/day (fixed dose)	MC, NI, OL, Randomized SGA prepubertal pediatric patients with a bone age ≤9 years for girls and ≤10 years for boys	N=194 1 year	Primary: Change from baseline in height SDS at one year Secondary: Safety	Primary: There were significant gains in mean height SDS after one year of treatment in both the fixed dose and individualized dose groups (1.13 and 0.89 SDS; P<0.001 for both). The fixed dose group had a significantly greater change in height SDS compared to the individualized dose group (least mean square difference, -0.24; 95% CI, -0.35 to -0.12; P<0.001). There was no significant between group difference in change of height SDS in the low-dose individualized dose and high-dose individualized

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs somatropin (Humatrope®) 0.035 mg/kg/day for 3 months then either increase to 0.067 mg/kg/day if predicted 1 year change in height SDS was <0.75 or continue at 0.035 mg/kg/day if predicted 1 year change in height SDS was ≥0.75 (individualized dose)	and height SDS ≤-3			dose groups (least mean square difference, 0.03; 95% CI, -0.13 to 0.18). Secondary: There were no differences in adverse events reported in the treatment groups. The most common adverse events were nasopharyngitis, pyrexia, vomiting and headache.
Bozzola et al.[77] (2004) Somatropin (Genotropin®) 0.23 mg/kg/week for 2 years (Group A) vs somatropin (Genotropin®) 0.23 mg/kg/week for 1 year, followed by somatropin 0.46 mg/kg/week (Group B)	OL SGA pediatric patients 2 to 7 years of age	N=26 2 years	Primary: Growth response Secondary: Not reported	Primary: During year one, growth velocity significantly increased in both groups (P<0.0001). There was a significant decrease in growth velocity during year two in Group A (P<0.015), but Group B maintained their growth rate. In Group A, height SDS significantly increased compared to baseline during years one and two (P<0.000002 and P<0.000001). In Group B, height SDS also increased significantly compared to baseline during years one and two (P<0.000001 and P<0.000001). There was a greater increase in height gain with the patients in Group B compared to the patients in Group A (P<0.02). Secondary: Not reported
de Zegher et al.[78] (2005)	MA (4 OL, RCTs)	N=82	Primary: Change in height	Primary: In patients who received at least seven years of treatment with somatropin,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin 33 µg/kg/day (low-dose group) vs somatropin 67 µg/kg/day (high-dose group) vs placebo or no treatment	Prepubertal pediatric patients who were diagnosed with SGA and failed to have catch-up growth during infancy	Mean duration of 10 years	SDS Secondary: Not reported	those who received high-dose somatropin had an additional height gain by 0.38 SDS compared to those who received low-dose somatropin (95% CI, 0.06 to 0.69; P=0.019). Secondary: Not reported
Crabbe et al.[79] (2008) GH 33 µg/kg/day (low-dose group) vs GH 67 µg/kg/day (high-dose group) vs placebo or no treatment	MA Pediatric patients diagnosed with SGA or IUGR	N=not reported 2 years	Primary: Change in height SDS Secondary: Not reported	Primary: At two years, the high-dose group had a greater gain in height SDS by 0.48±0.35 compared to the low-dose group (P value not reported). Secondary: Not reported
de Zegher et al.[80] (1996) Somatropin 0.033 mg/kg/day vs	MA (4 OL, RCTs) Prepubertal pediatric patients between 2 and 8 years of age who had a birth weight	N=244 2 years	Primary: Height velocity, change in height SDS Secondary: Change in weight,	Primary: Due to differences in baseline characteristics, data from one study conducted in France was analyzed separately from the other three studies. In three of the trials, there was a dose-dependent response in height velocity and an increase in height SDS at two years. Height velocity at two years was 5.59±0.14, 8.26±0.20, 9.88±0.18 and 11.38±0.30 cm/year in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin 0.067 mg/kg/day vs somatropin 0.1 mg/kg/day vs placebo or no treatment	or length <-2 SDS for gestational age or height for age <-0.2 SDS and who had never received GH treatment		change in bone age	untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (P<0.005). The increase in height SDS was 0.12±0.07, 1.13±0.09, 2.11±0.10 and 2.64±0.16 in the untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (P<0.005). Similarly, a dose-dependent response in height velocity and change in height SDS was seen in the French study. The height velocity was 5.54±0.27, 7.46±0.11 and 8.15±0.17 cm/year in the untreated, 0.033 mg/kg/day and 0.067 mg/kg/day groups, respectively (P<0.05). The increase in height SDS was 1.33±0.07, 1.04±0.05 and 0.17±0.10 in the untreated, 0.033 mg/kg/day and 0.067 mg/kg/day groups, respectively (P<0.005). No one in the French study received somatropin at 0.1 mg/kg/day. Secondary: There was a dose-dependent increase in weight in all four studies (P<0.05). Annual bone age increment did not differ significantly across all three groups in the French study. In the other three studies, however, there was a dose-dependent response with the bone age increment, which was 0.85±0.06, 1.00±0.06, 1.20±0.06 and 1.41±0.13 years for the untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (P<0.005).
Growth Hormone Deficiency In Children				
Thornton et al.[81] (2021) heiGHt Lonapegsomatropin-tcgd (Skytrofa®) 0.24 mg/kg SC once weekly vs somatropin (Genotropin®) 0.034 mg/kg SC once daily	AC, MC, OL, PG, RCT Treatment-naïve patients (males three to twelve years of age, females three to eleven years of age) at Tanner stage 1 with GHD (either isolated or as part of multiple pituitary hormone deficiency) who	N=161 52 weeks	Primary: Annualized height velocity Secondary: Annualized height velocity SDS, IGF-1, IFG-1 SDS, IGFBP-3, IGFBP-3 SDS, bone age	Primary: Least squares mean (standard error) annualized height velocity at 52 weeks was 11.2 (0.2) cm/year for lonapegsomatropin-tcgd vs 10.3 (0.3) cm/year for daily somatropin (P=0.009), with lonapegsomatropin-tcgd demonstrating both noninferiority and superiority over daily somatropin. Secondary: Least squares mean (standard error) height SDS increased from baseline to week 52 by 1.10 (0.04) vs 0.96 (0.05) in the weekly lonapegsomatropin-tcgd vs daily somatropin groups (P=0.01). Least squares mean (standard error) IGF-1 SDS increased by 0.72 (0.09) vs -0.02 (0.12) in the weekly lonapegsomatropin-tcgd vs daily somatropin groups (P<0.0001). No statistically significant differences were observed for other secondary endpoints.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	have a height SDS ≤ -2.0, IGF-1 SDS ≤ -1.0, BMI within ±2.0 SD of the mean, and bone age ≥6 months behind chronological age			
Maniatis et al.[82] (2022) fliGHt Lonapegsomatropin-tcgd (Skytrofa®) 0.24 mg/kg SC once weekly	MC, OL, SA Male and female patients aged six months to 17 years old at Tanner stage <5 with GHD who were previously treated with daily somatropin for 13 to 130 weeks	N=143 26 weeks	Primary: Treatment emergent adverse events Secondary: Annualized height velocity, height SDS, IGF-1 SDS	Primary: Over half of the subjects (57%) experienced at least one adverse event, with 4% experiencing an adverse event that was assessed by the investigator as related to study drug. Less than half of patients experienced adverse events that were mild (45%) or moderate (12%) in severity. The most common adverse events were pyrexia (12%), nasopharyngitis (10%), upper respiratory tract infection (10%), headache (8%), and oropharyngeal pain (5%). One patient experienced a serious adverse event. No patients discontinued study drug due to an adverse event. Secondary: The least squares mean (standard error) annualized height velocity was 8.72 (0.24) cm/year at week 26. The observed mean (SD) height SDS increased from -1.40 (0.83) at trial enrollment to -1.15 (0.82) week 26. After switching to lonapegsomatropin-tcgd, the least squares mean (standard error) for average IGF-1 SDS was at 1.62 (0.10) and 1.65 (0.11) at week 13 and week 26, respectively, which increased from 0.91 (1.25) at baseline.
Kriström et al.[83] (2009) GH 17 to 100 µg/kg/day based on predicted growth response (individualized-dose group) vs	MC, OL, RCT Pediatric patients between 3 and 11 years of age for boys or between 3 and 10 years of age for girls who had isolated GHD or ISS with a height SDS ≤-2 or growth velocity SDS ≤-1	N=153 2 years	Primary: Difference between current height SDS and target height SDS Secondary: Changes in mean height SDS, changes in bone age, safety	Primary: At two years, the mean difference between current height SDS and target height SDS was -0.42±0.46 in the individualized-dose group and -0.48±0.67 in the standard-dose group (P=0.003). The range in distribution of this difference was 32% narrower in the individualized-dose group compared to the standard-dose group, demonstrating a more consistent treatment response to GH with an individualized-dose regimen. Secondary: The mean gain in height SDS was 1.32 in both treatment groups (P>0.05). There was no difference between patients with GHD and those with ISS with regard to change in height SDS.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 43 µg/kg/day (standard-dose group)	and whose current height SDS was ≥1 SDS below target height SDS			Change in bone age delay was similar between the individualized- and standard-dose groups (0.52 and 0.41 years, respectively; P>0.05). Incidence of adverse events was similar between the two groups. No serious adverse events related to GH were reported. There were no significant changes in fasting blood glucose and HbA1c. Fasting serum insulin levels increased significantly from baseline in both groups. Increase in serum IGF-1 levels was comparable between the two groups. Nine children in the individualized-dose group and five children in the fixed-dose group had serum IGF-1 levels above 3 SDS.
Wilson et al.[84] (1985) GH IM TIW vs GH SC TIW	OL, RCT Pubertal and prepubertal pediatric patients between 5.7 and 18.3 years of age with GHD and who had not received GH in the previous 2 weeks	N=20 6 months	Primary: Growth velocity and presence of anti-GH antibodies Secondary: Changes in serum IGF-1 and IGF-2 levels	Primary: There was no significant difference in growth velocity at six months in the IM (6.1±2.8 cm/year) and SC (4.9±2.0 cm/year) groups. Anti-GH antibodies were positive in one patient in the SC group prior to study; the titer decreased from log 1.5 to 1.0 during the study. One patient from each group developed anti-GH antibodies during the study. The presence of anti-GH antibodies had no major effect on growth. Secondary: Changes in serum IGF-1 and IGF-2 levels were not significantly different between the two groups.
Coelho et al.[85] (2008) Somatropin (Genotropin®) 15 IU/m^2/week SC daily (standard-dose group) vs somatropin (Genotropin®) 30 IU/m^2/week SC	OL, RCT Prepubertal pediatric patients with GHD who had been receiving GH 15 IU/m^2/week SC daily for at least 1 year	N=49 Mean duration 5.86±1.62 years (treatment was discontinued once final height was reached)	Primary: Change in height SDS Secondary: Age at end of treatment and at mid-puberty	Primary: Change in height SDS at the end of treatment was similar between the high- and standard-dose groups (1.2±1.2 and 1.1±1.7, respectively; P=0.81). The final height SDS was also similar between the two groups (-0.71±1.3 and -0.87±1.1; P=0.3). Secondary: Patients receiving the standard-dose regimen were older at the end of treatment compared to those receiving the high-dose regimen (17.2±1.7 vs 16.1±1.5 years; P=0.026), but the mean age at mid-puberty was similar between the two groups (P=0.3).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily (high-dose group)				
Shih et al. (abstract)[86] (1994) Somatropin (Genotropin®) 0.1 IU/kg/day SC daily vs somatropin (Humatrope®) 0.1 IU/kg/day SC daily vs somatropin (Saizen®) 0.2 IU/kg/day SC TIW	RCT Prepubertal pediatric patients with GHD	N=15 12 months	Primary: Change in bone age, height velocity, height SDS and anti-GH antibody titers; safety Secondary: Not reported	Primary: The average bone age increased by 0.8±0.2 years in the Genotropin® group, 0.8±0.7 years in the Humatrope® group and 2.1±1.3 years in the Saizen® group. The mean height velocity increased from 3.4±0.7 to 11.3±2.0 cm/year with Genotropin®, from 4.0±1.3 to 9.4±1.9 cm/year with Humatrope® and from 3.7±1.2 to 11.1±3.3 cm/year with Saizen®. Similarly, the height SDS increased from -4.0±0.5 to -2.7±0.7 in the Genotropin® group, from -2.9±0.7 to -2.2±1.0 in the Humatrope® group and -4.2±3.1 to -3.1±2.9 in the Saizen® group. There were no differences among the three treatment groups with regard to change in bone age, height velocity and height SDS (P values not reported). Anti-GH antibody titers were detected in one patient in the Saizen® group and one patient in the Genotropin® group. The presence of anti-GH antibodies did not affect height velocity. One patient developed subclinical hypothyroidism. No other adverse events were noted in the other patients. Secondary: Not reported
de Muinck Keizer-Schrama et al.[87] (1992) Somatropin (Norditropin®) 2 IU/m^2/day SC (standard-dose group)	MC, RCT Prepubertal pediatric patients with GHD of organic or idiopathic origin and a bone age <12 years for boys and	N=38 (21 treatment-naïve and 17 treatment-experienced patients) Up to 2 years (treatment was	Primary: Changes in height velocity, height velocity SDS and height SDS Secondary: Change in, serum IGF-1 levels, BP,	Primary: In treatment-naïve patients, the increase in height velocity at one year was nonsignificantly greater with the high-dose regimen compared to the low-dose regimen (8.0 vs 5.5 cm/year; P>0.05). Similar trends were seen in changes in height velocity SDS and height SDS (9.76 vs 7.25; P>0.05, 1.56 vs 1.16; P>0.05, respectively). In treatment-experienced patients who had been receiving standard-dose somatropin for at least one year prior to the study, there was an increase in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs somatropin (Norditropin®) 4 IU/m^2/day SC (high-dose group)	<10 years for girls and who were either treatment-naïve or treatment-experienced to GH	discontinued once adult height was reached)	thyroid function, anti-GH antibodies, lipid profile, HbA1c and other laboratory values	height velocity in the high-dose group and a decrease in the standard-dose group after two years of treatment (0.7 vs -1.0 cm/year; P<0.005). Similarly, the improvement in height velocity SDS was seen in the high-dose group but not in the standard-dose group (1.39 vs -0.73; P<0.01). Increase in height SDS at two years was also greater in the high-dose group compared to the standard-dose group (1.91 vs 0.69; P<0.01). Secondary: Serum IGF-1 levels increased significantly from baseline in both groups, with no significant intergroup differences. No clinically significant changes were seen in BP in both groups. Two patients from the high-dose group had subnormal T_4 and low TSH levels but had no clinical signs of hypothyroidism. One treatment-naïve patient in the high-dose group developed anti-GH antibodies, which became undetectable after 12 months of treatment. A nonsignificant decrease in cholesterol, LDL and apo-B was seen in both groups. No significant changes were seen in HbA1c, hemoglobin, hematocrit, platelet count, urea nitrogen, creatinine and alkaline phosphatase.
Sas et al.[88] (2010) Somatropin (Norditropin®) 2 IU/m^2/day SC (standard-dose group) vs somatropin (Norditropin®) 4 IU/m^2/day SC (high-dose group)	MC, RCT Prepubertal pediatric patients with GHD of organic or idiopathic origin and a bone age <12 years for boys and <10 years for girls and who were either treatment-naïve or treatment-experienced to GH	N=35 (20 treatment-naïve and 15 treatment-experienced patients) Study duration not specified (treatment was discontinued once adult height was reached)	Primary: Difference between adult height SDS and target height SDS Secondary: Adult height SDS, change in height SDS, number of patients whose height was at or above the lower limit of the target height range, duration of treatment, onset of	Primary: The difference between adult height SDS and target height SDS was nonsignificantly smaller in the high-dose group compared to the standard-dose group in both treatment-naïve (-0.3±1.0 and -0.7±0.9, respectively; P=0.29) and treatment-experienced patients (0.1±1.1 vs -0.6±0.9, respectively; P=0.18). Secondary: Adult height SDS with high- and standard-dose groups was -1.4±1.1 and -1.5±0.9, respectively, in treatment-naïve patients (P=0.75) and 0.0±1.1 and -0.6±0.6, respectively, in treatment-experienced patients (P=0.24). The onset of puberty was 1.1 years earlier in patients receiving high-dose somatropin compared to those receiving standard-dose somatropin (95% CI, 0.1 to 2.1; P=0.04). There were no significant differences between the two groups with regard

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			puberty, bone maturation, safety	to change in height SDS, the number of patients whose height was at or above the lower limit of the target height range, duration of treatment with somatropin and bone maturation. Treatment was well-tolerated, with no report of diabetes.
Cohen et al.[89] (2002) Somatropin (Norditropin®) 0.025 mg/kg/day SC (low-dose group) vs somatropin (Norditropin®) 0.05 mg/kg/day SC (medium-dose group) vs somatropin (Norditropin®) 0.1 mg/kg/day SC (high-dose group)	RCT Prepubertal pediatric patients with GHD and a bone age <9 years for boys and <8 years for girls and who had never received GH treatment	N=111 2 years	Primary: Change in height SDS Secondary: Changes in serum IGF-1 and IGFBP-3 SDS; changes in bone age, fasting blood glucose, HbA1c, fasting plasma insulin, safety	Primary: In all three groups, height SDS increased significantly from baseline at two years. Patients in the low-dose group had significantly smaller gain in height SDS compared to the medium- and high-dose groups (P<0.01). When stratified by gender, a dose-dependent response was seen in boys but not in girls. Secondary: There was a dose-dependent increase in serum IGF-1 and IGFBP-3 levels and SDS (P<0.05). Bone age advancement was higher with the medium- (1.2±1.0 years) and high-dose groups (1.2±0.9 years) compared to the low-dose group (0.7±0.7 year; P value not reported). No significant differences were seen in fasting blood glucose and HbA1c across the three groups, while there was a dose-dependent increase in fasting insulin levels at one year (P<0.001) but not at two years (P=0.08). Rates of adverse events were similar across all three groups. Anti-GH antibodies were detected in significant levels in 12% of the patients with no correlation to dose or growth response.
MacGillivray et al.[90] (1996) Somatropin (Nutropin®) 0.3 mg/kg/week SC TIW vs	MC, RCT Prepubertal pediatric patients with GHD and a bone age ≤10 years for girls and ≤11 years for boys and who had never received GH	N=65 4 years	Primary: Annual growth velocity, cumulative change in height and height SDS Secondary: Changes in bone age and age at onset of puberty	Primary: Patients were excluded from statistical analyses once they had reached puberty. The number of patients remaining prepubertal at one, two, three and four years was 51, 40, 26 and 23, respectively. The annual growth velocity was significantly greater with daily dosing compared to TIW dosing throughout the study. The growth velocity at four years was 7.5±1.4 and 6.0±1.3 cm/year in the daily and TIW groups, respectively (P=0.037).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Nutropin®) 0.3 mg/kg/week SC administered in daily doses	treatment			The cumulative change in height was also significantly greater in the daily group (38.4±5.5 cm) compared to the TIW group (28.7±3.2 cm; P=0.0002). Patients receiving daily dosing gained an additional 1.7 height SDS than patients receiving TIW dosing at four years (P=0.0003). Secondary: Gain in bone age was similar between the two groups (P=0.84). The mean chronological age at the onset of puberty was also similar between the two groups (P=0.84).
Mauras et al.[91] (2000) Somatropin (Nutropin®) 0.7 mg/kg/week SC (high-dose group) vs somatropin (Nutropin®) 0.3 mg/kg/week SC (standard-dose group)	MC, RCT Pubertal pediatric patients between 10 and 18 years of age for boys and between 8 and 16 years of age for girls who had GHD with a bone age ≥14 years for boys and ≥12 years for girls and who had been receiving GH for at least 6 months	N=97 Up to 63 months (treatment was discontinued once adult height was reached)	Primary: Near-adult height and height SDS Secondary: Last measured height, height SDS, growth velocity, mean age and bone age at near-adult height, duration of therapy, change in body weight, BMI, bone age, Tanner pubertal stage, lumbar spine BMD, total body BMC, serum IGF-1 levels, HbA1c, fasting blood glucose, fasting insulin and safety	Primary: A total of 75 patients reached near-adult height, with 42 patients in the standard-dose group and 33 patients in the high-dose group. Patients in the high-dose group attained higher near-adult height by 4.6 cm (95% CI, 2.6 to 6.5; P<0.001) compared to patients in the standard-dose group. Height SDS at near-adult height was 0.0±1.2 in the high-dose group and -0.7±0.9 in the standard-dose group (P=0.002). There was a significantly greater gain in height SDS with the high-dose regimen compared to the standard-dose regimen (1.1±1.0 vs 0.6±0.8; P=0.012). Secondary: Patients in the high-dose group were taller at last measured height by 2.8 cm (95% CI, 0.2 to 5.3; P=0.036) compared to the standard-dose group. At 36 months, the height SDS was higher in the high-dose group compared to the standard-dose group (1.4±0.8 vs 0.9±0.7; P=0.023). Growth velocity was higher with high-dose somatropin compared to standard-dose somatropin during 0 to 12 months (9.8 vs 8.2 cm/year; P=0.001) and during 24 to 36 months (difference, 1.7 cm/year; P=0.038). There were no differences between the two groups with regard to mean age and bone age at near-adult height, duration of therapy, body weight, BMI, bone age, Tanner pubertal stage, lumbar spine BMD and total body BMC.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a greater increase in serum IGF-1 levels in the high-dose group compared to the standard-dose group, although this difference did not reach statistical significance. No significant changes were seen in HbA1c and fasting blood glucose in both groups. Fasting insulin increased to a greater extent in the high-dose group than the standard-dose group at 24 months (P=0.011). Incidence of adverse events was similar between the two groups. One case of worsening scoliosis requiring surgery was reported in each group. One case of hip pain, which was considered possibly related to the study drug, was reported in the high-dose group.
Romer et al.[92] (2009) Somatropin lyophilisate (Omnitrope®) 0.03 mg/kg/day SC for 15 months, followed by somatropin liquid (Omnitrope®) 0.03 mg/kg/day SC (Group A) vs somatropin lyophilisate (Genotropin®) 0.03 mg/kg/day SC for 9 months, followed by somatropin liquid (Omnitrope®) 0.03 mg/kg/day SC (Group B)	MC, OL, RCT Prepubertal pediatric patients between 2 and 14 years of age who had growth failure secondary to idiopathic GHD and who had never had GH treatment	N=89 7 years	Primary: Height, height SDS, height velocity, height velocity SDS, IGF-1, IGFBP-3, safety Secondary: Not reported	Primary: Forty-nine out of 89 patients completed seven years of treatment. In these patients, the mean height at the end of seven years was 155.3±10.86 cm. At seven years, the mean height SDS increased from -3.06±0.80 at baseline in both treatment groups to -0.78 in Group A and -1.01 in Group B. The mean difference in height SDS between the two groups was 0.13 (95% CI, -0.04 to 0.31) at nine months, 0.14 (95% CI, -0.09 to 0.37) at 15 months and 0.25 (95% CI, -0.33 to 0.83) at seven years. In both groups, the mean height velocity increased from 3.84±1.03 cm/year at baseline to 12.01±4.01 cm/year at three months and slowly declined to 5.53 cm/year at seven years. Height velocity at any point in the study was significantly higher compared to baseline. The mean difference in height velocity between Groups A and B was -0.19 cm/year (95% CI, -1.34 to 0.95) at nine months, -0.14 cm/year (95% CI, -0.98 to 0.70) at 15 months and -0.07 cm/year (95% CI, -1.43 to 1.29) at seven years. At seven years, the mean height velocity SDS increased from -2.27±1.09 at baseline to 6.84±4.63 at three months and then decreased to -0.18 in Group A and 0.11 in Group B. Height velocity SDS at any point in the study was significantly higher compared to baseline. The mean difference in height velocity SDS between the two groups was 0.79 (95% CI, -0.56 to 2.15) at nine months, 0.76 (95% CI, -0.37 to 1.90) at 15 months and -0.37

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dose was readjusted to body weight after 6 months and then at each scheduled study visit. Treatment was continued until satisfactory height was reached or when epiphyseal fusion had occurred.				(95% CI, -2.02 to 1.28) at seven years. The mean serum IGF-1 SDS was -1.84±0.57 at baseline, and the values in both treatment groups were higher compared to baseline at any point in the study. The serum IGF-1 levels between the two groups were not significantly different at any time point during the study (values not reported). The mean serum IGFBP-3 levels at any time point were significantly higher than baseline in both groups. The difference between the two groups was not significant at any time point, with the exception of 48 months, in which the difference was -0.46 (95% CI, -0.86 to -0.07). A total of 1,759 adverse events were reported, out of which 323 were study drug-related. There were no clinically relevant differences between the two groups in terms of frequency, distribution, intensity and outcome of these adverse events. The rate of adverse drug events per patient-year was 0.478, 0.576 and 0.849 for Omnitrope® lyophilisate, Omnitrope® liquid and Genotropin® lyophilisate, respectively. Adverse drug events occurring at a rate of least 0.05 events per patient year with any agent were hypothyroidism, decreased TSH, increased HbA1c, increased TG, eosinophilia, headache and injection site hematoma. The rate of glucose-related adverse drug events was 0.078 with Omnitrope® and 0.059 with Genotropin®. One patient experienced worsening of scoliosis. There were no study withdrawals due to adverse events and no relevant changes in vital signs or clinical laboratory data. Secondary: Not reported
Idiopathic Short Stature				
Kriström et al.[93] (2014) GH (Genotropin®) 0.033 mg/kg/day vs	MC, RCT Patients without GHD with height below -2 SDS, chronological age was eight to 13	N=151 Treated until adult height (average duration not specified)	Primary: IGF-1, IGFBP3, growth response measured by change in height SDS until adult height	Primary: In the all-subject per-protocol population, All_{PP} (N=108) control group, the mean IGF-1 SDS and IGFBP3 SDS increased during the study relative to baseline by 0.31 (P<0.001) and 0.21 (P<0.05), respectively. The change in IGF-1 SDS was significantly higher (P<0.001) in the all-subject per-protocol population GH-treated groups: 1.20 for GH 0.033

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Genotropin®) 0.067 mg/kg/day vs no GH	years for girls and ten to 15 years for boys, corresponding bone age of 11 years of younger (girls) and 13 years of younger (boys)		Secondary: Not reported	mg/kg/day dose and 2.07 for GH 0.067 mg/kg/day dose versus no GH treatment, 0.31. For the ISS populations, the corresponding correlation coefficients for the $IGF\text{-}1_{SDS}$ and for $IGFBP3_{SDS}$ were −0.46 and −0.49 for the children with ISS included in the intent-to-treat population (ISS_{ITT}) and −0.37 and −0.40 for the ISS_{ITT}, respectively (all P<.001). The change in IGF-1 SDS and gain in height SDS were correlated in the All_{PP} GH-treated population (P<0.0001) as well as the total All_{PP} population (P<0.0001). The IGF-1 SDS study level did not correlate with gain in height SDS for the All_{PP} GH-treated group (P was not significant) but did for the total All_{PP} population (P<0.002). Secondary: Not reported
van Gool et al.[94] (2010) GH 0.5 or 1 mg/m^2/day for 3 months; a 3 month washout period; XO to 0.5 to 1 mg/m^2/day; a 3 month washout; followed by 2 mg/m^2/day for 2 to 5 years until the onset of puberty vs no treatment	RCT Patients with ISS, height <-2 SDS, age 4 to 8 years for girls and 4 to 10 years for boys, peak GH >10 µg/L after provocative stimulation test and normal sitting height	N=40 5 to 12 years	Primary: Adult height Secondary: Not reported	Primary: The mean duration of GH treatment was 3.3 years. At discontinuation of treatment, there was a significant increase in height SDS with GH-treated patients compared to controls (P=0.001). There were no significant between groups differences in adult height SDS and adult height minus starting height SDS (P=0.6 and P=0.8). Secondary: Not reported
Albertsson-Wikland et al.[95] (2008) Somatropin	RCT Patients with height <-2 SDS, chronological age 7	N=108 ≥1 year	Primary: Final height, gain in height SDS, difference of final height and mid-	Primary: Compared to untreated controls, patients with ISS treated with somatropin 67 µg/kg/day had a significantly greater final height in boys (P=0.001) and girls (P=0.018). The gain in height SDS was significantly greater than controls in both the 33 and 67 µg/kg/day groups (P=0.004 and P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Genotropin®) 33 µg/kg/day (prepubertal patients) vs somatropin (Genotropin®) 67 µg/kg/day (prepubertal and pubertal) vs no treatment (prepubertal and pubertal)	to 13 years and bone age ≤11 years in girls and chronological age 10 to 15 years and bone age ≤13 years in boys		parental height Secondary: Not reported	The difference in final height and mid-parental height was greater in the 67 µg/kg/day group compared to controls (P=0.001). Only the difference in final height and mid-parental height was significantly different comparing the 33 and 67 µg/kg/day groups (-0.1 vs 0.4; P=0.042). Secondary: Not reported
Hopwood et al.[96] (1993) First 12 months: somatropin 0.1 mg/kg TIW vs no treatment Months 24 to 36 (re-randomization to): somatropin 0.3 mg/kg/day vs somatropin 0.3	RCT Patients <3rd percentile for height (<-1.88 SD), prepubertal, bone age <9 years for girls or <10 years for boys and GH >10 µg/L after provocative stimulation test	N=121 36 months	Primary: Mean growth rate, height SDS Secondary: Not reported	Primary: During the first year, patients treated with somatropin once daily had a significantly higher growth rate than patients treated with somatropin TIW (9.0±1.6 vs 7.8±1.2 cm/year; P<0.0005). During years two and three, there were no significant differences between groups in growth rate. The change in height SDS was significantly greater with once daily compared to TIW dosing (1.2±0.5 vs 1.0±0.6; P<0.04). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/kg TIW				
Kriström et al.[97] (2009) GH 43 µg/kg/day (standard dose) vs GH 17 to 100 µg/kg/day based on prediction model (individualized dose)	OL, RCT Patients with GHD or ISS who were prepubertal, 3 to 10 years of age for girls and 3 to 11 years of age for boys, height <-2 SDS or growth velocity <-1 SDS, ≤- 1 SDS below mid-parental height and born at gestational age >30 weeks	N=153 2 years	Primary: Range of distribution for difference between current height SDS and mid-parental height SDS Secondary: Height SDS	Primary: After two years, the range of distribution for difference between current height SDS and mid-parental height SDS was significantly reduced by 32% in the individualized dose group compared to the standard dose group (P=0.003). The mean values for difference between current height SDS and mid-parental height SDS were not significantly different (-0.42±0.46 for individualized and -0.48±0.67 for the standard dose). Secondary: After two years, there was no significant differences in height SDS for each group compared to baseline (P=NS).
Wit et al.[98] (2005) GH 0.24 mg/kg/week vs GH 0.24 mg/kg/week for 1 year, followed by GH 0.37 mg/kg/week vs GH 0.37 mg/kg/week	ES, OL, randomized (2 years) Prepubertal patients ≥5 years with ISS with height <-2 SDS, bone age <10 years in girls and <12 years in boys, height velocity <25th percentile, GH >10 µg/L after provocative stimulation test and normal thyroid function or adequate thyroid replacement	N=239 >2 years (until final height)	Primary: Height velocity and final height Secondary: Not reported	Primary: After two years, height velocity was significantly higher with GH 0.37 mg/kg/week compared to 0.24 mg/kg/week and 0.24 to 0.37 mg/kg/week (treatment difference, 0.8 cm/year; P=0.003 and treatment difference, 0.9 cm/year; P=0.001, respectively). Duration of treatment was not significantly different between treatment groups. The mean between-dose effect on final height SDS was 0.57±0.25 SDS (3.6 cm; P=0.025). There were significant differences between final height and baseline with 0.24 mg/kg/week (P≤0.001) and 0.37 mg/kg/week (P≤0.001). Final heights were within normal ranges for 94% of patients with 0.37 mg/kg/week and 71% with 0.24 mg/kg/week. Secondary: Not reported
Finkelstein et al.[99] (2002)	MA (10 controlled trials; 28	N=434 (controlled	Primary: Effect of GH on	Primary: Controlled trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 0.14 to 0.4 mg/kg/week	uncontrolled trials) Pediatric patients with absence of GHD, with no previous GH treatment, without comorbid condition that impair growth and without previous treatment with sex steroids or anabolic agents	trials) >6 months	growth velocity and height SDS at one year and on adult height Secondary: Not reported	After one year, growth velocity with GH was significantly greater than controls (mean between group difference, 2.86±0.37 cm/year; 95% CI, 2.13 to 3.59). In the subset of five RCTs, growth velocity after one year was significantly greater with GH compared to controls (between group difference, 2.53 cm/year; 95% CI, 1.72 to 3.35). The change in growth velocity compared to baseline in the GH treated patients was 3.63±0.32 cm/year (95% CI, 3.00 to 4.25). In the control group the change in growth velocity compared to baseline was 0.93±0.35 cm/year (95% CI, 0.25 to 1.62). After one year, the childhood height SDS was significantly greater with GH compared to controls (mean between group difference, 0.60±0.37 SD; 95% CI, 0.26 to 0.95). The adult height SDS was significantly greater in the GH group compared to the placebo group (weighted aggregate between group difference, 0.84±0.19 SD (95% CI, 0.46 to 1.22). The pooled estimate for adult height SDS was -1.51 SD (95% CI, -1.70 to -1.32) with GH compared to -2.29 SD (95% CI, -2.63 to -1.96) with controls. Uncontrolled trials After one year, the pooled estimate for growth velocity was 7.57±0.30 cm/year (95% CI, 4.00 to 4.59) compared to 4.29±0.15 cm/year (95% CI, 6.99 to 8.19) at baseline. The childhood height SDS was -2.62±0.09 SD (95% CI, -2.79 to -2.44) at baseline and -2.19±0.10 SD (95% CI, -2.39 to -1.99) after one year of treatment. The mean predicted adult height was -2.18±0.17 SD (95% CI, -2.52 to -1.85) compared to an achieved height of -1.62±0.07 SD (95% CI, -1.77 to -1.47) with GH. Secondary: Not reported
Bryant et al.[100] (2007)	MA (10 RCT)	N=741	Primary: Final height	Primary: In the one trial that reported near final height, patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin vs placebo vs no treatment	Pediatric patients with ISS and normal GH secretion	>6 months	Secondary: Short term growth, quality of life, adverse effects and cost	somatropin were significantly taller than controls with no treatment or controls that did not consent to randomization (155.3±6.4 vs 147.8±2.6 and 149.3±3.3 cm; P=0.003). Near final height SDS was significantly higher in the somatropin group compared to controls and non-consent groups (-1.14±1.06 SDS vs -2.37±0.46 and -2.13±0.55; P=0.004). In one trial that reported adult height SDS, patients treated with somatropin had a significantly greater adult height by 0.57 SDS compared to patients treated with placebo (3.7 cm; 95% CI, 0.03 to 1.10; P<0.04). Secondary: One trial demonstrated a significantly greater change in height SDS at one year with somatropin-treated patients compared to untreated controls (WMD, 0.90 SDS; 95% CI, 0.33 to 1.47; P<0.05). Another trial demonstrated a significant change from baseline at one year with somatropin (P<0.05) compared to no change with placebo. In two trials no significant differences between treated and untreated groups. One trial showed a significant increase at two years in height SDS with somatropin compared to controls (P<0.001). Finally, another trial demonstrated a significant change in height SDS compared to no change in untreated controls (P<0.0.001). In the MA of three trials reporting growth velocity at one year, somatropin-treated patients had a significantly greater growth velocity compared to untreated controls (WMD, 2.48; 95% CI, 2.06 to 2.90; P<0.00001). In another study, growth velocity at three years was significantly higher with somatropin compared to untreated controls (6.4 vs 5.2 cm/year; P<0.003). One study did not find a significant difference between treated and untreated patients (P=0.21). Growth velocity SDS was significantly greater at one year with somatropin-treated prepubertal patients (P<0.0.001) and pubertal patients (P<0.05) compared to untreated controls, and at six months in somatropin pubertal patients compared to placebo (P<0.0001). There were no significant differences in quality of life between somatropin-treated patients and controls.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no serious adverse effects reported.
Growth Hormone Deficiency In Adults				
Gonzalez et al.[101] (2017) rhGH 0.4 mg daily SC vs placebo Treated for 12 weeks, underwent washout for two weeks, and then crossed over to the alternative treatment for 12 weeks	DB, OL, PC, RCT, XO Patients with severe adult-onset growth hormone deficiency	N=17 6 month DB followed by 6 month OL	Primary: Left ventricular mass Secondary: Cardiac function and exercise capacity	Primary: At baseline, patients with adult-onset growth hormone deficiency had a significantly higher systolic blood pressure (P=0.04), ejection fraction (P=0.009), stroke volume (P=0.05), and left ventricular mass (0.003) than the control group. Secondary: Treatment with rhGH normalized the IGF-1 concentration without an effect on exercise capacity, cardiac structure, or cardiac function during either the cross-over phase or the open-label extension phase.
van Bunderen et al.[102] (2018) GH daily SC with IGF-1 target level of -1 to- 2 SDS (low dose) vs GH daily SC with IGF-1 target level of 1 to 2 SDS (high dose)	OL, RCT Adult patients with severe GHD and more than one year of treatment with an IGF-1 level between -1 and 1 SDS, and stable for at least six months	N=32 24 weeks	Primary: Memory and wellbeing Secondary: Not reported	Primary: Post hoc tests indicated a significant lower Spatial Working Memory (SWM) Total Errors score of the females in the LD group at week 24 as compared to baseline, P=0.009. No significant effect was found in males. This result indicates that females in the low-dose group perform better on the SWM task after 24 weeks of treatment compared to the high dose group, and compared to baseline. Post hoc tests did not indicate a significant lower SWM Strategy score of the females in the low dose or in the high dose group at week 24 as compared to baseline (P>0.05). This result indicates that females in the low dose group had a better working memory after 24 weeks of treatment compared to the high dose group. The Profile of Moods States (POMS) questionnaire was used to assess mood and measured depression, anger, fatigue, tension, and vigor. With respect to scores for anger, depression, and tension, no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				differences were found between males and females, or low dose or high dose groups. With respect to fatigue, post hoc tests did not indicate any significant difference in fatigue score of the females in the low dose or the high dose group at week 24 as compared to baseline (P>0.05). Females within the low dose group showed a higher increase in fatigue after 24 weeks of treatment relative to females in the high dose group. With respect to vigor, analyses were performed separately for males and females. In the males, no significant interaction effect was found (P> 0.05); however, in females, a significant interaction was found (P=0.001). Post hoc tests indicated a significant lower vigor score of the females in the low dose group at week 24 as compared to baseline (P=0.02). Overall, the low dose group females experienced more fatigue and less vigor compared to the females in the high dose group. Secondary: Not reported
Van Bunderen et al.[103] (2016) GH daily SC with IGF-1 target level of -1 to- 2 SDS (low dose) vs GH daily SC with IGF-1 target level of 1 to 2 SDS (high dose)	OL, RC Adult patients with severe GHD and more than one year of treatment with an IGF-1 level between -1 and 1 SDS, and stable for at least six months	N=32 24 weeks	Primary: Metabolic changes (waist circumference, TC, HDLc, LDLc, TG), physical performance, tolerability Secondary: Not reported	Primary: The between-group analyses for change over time between the low dose and high dose groups. A significant (P<0.10) interaction for gender with dosing regimen was found for waist circumference, TC, and HDLc. These analyses were repeated after stratification for gender. A significant difference in effect on waist circumference between the low dose and high dose groups was observed in women (P=0.04), and for HDLc in men (P=0.02). Changes in total cholesterol were not significantly different for low dose or high dose group in men (P=0.40) or women (P=0.08). There was no significant difference between the groups in effect on muscle strength and physical performance. The LASA Physical Activity Questionnaire was analyzed for the subjects who reported representative data (9 versus 8 subjects). The difference between low dose and high dose groups were not significant for hand grip strength (P=0.94), physical activity measured in minutes per day (P=0.80), or the six-minute walk test (P=0.34). Both groups reported the same number of adverse events. Subjects in the low dose group reported more fatigue (80% of the women and 10% of the men). Subjects in the high dose group reported more myalgia (equally

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				distributed for women and men). None of the reported events led to a change of the GH dose. When asking the subject how they felt overall after 24 weeks, significantly more subjects answered to feel better in the high dose group (7 versus 1) and to feel worse in the low dose group (4 versus 2) (P=0.04). Secondary: Not reported
Chihara et al.[104] (2008) Somatropin (Genotropin®) 0.003 mg/kg/day SC for 8 weeks, then adjust by increment of up to 0.003 mg/kg/day according to serum IGF-1 levels	ES, OL Adult patients with GHD who previously participated in the 24 week DB, PC, RCT	N=71 48 weeks	Primary: Changes in body composition, lipid profile, symptom scores, SF-36 score, QoL-AGHDA score, safety Secondary: Not reported	Primary: In patients who previously received placebo in the DB phase, LBM increased significantly from 40.4±11.0 kg at baseline to 42.1±11.0 at 48 weeks (P=<0.0001) while fat mass was reduced significantly from 19.9±7.3 to 18.6±7.3 kg (P=0.0019). Moreover, there was a significant reduction in TC from 5.66±1.16 mmol/L at baseline to 5.39±1.05 mmol/L at 48 weeks (P=0.0181) as well as in LDL from 3.53±1.02 to 3.16±0.83 mmol/L (P=0.0018). HDL increased from 1.30±0.36 to 1.38±0.39 (P value not reported). In patients who previously received somatropin in the DB phase, LBM continued to increase during the OL phase from 43.9±10.3 kg at the end of DB phase to 44.4±10.4 kg at 48 weeks. Body fat mass increased slightly from 19.7±7.3 to 20.2±7.5 kg but still remained lower compared to the beginning of the PC phase (21.9±7.2 kg). Similarly, following a decrease in TC and LDL during the DB phase, there was an increase in both parameters during the ES phase, from 4.98±0.94 to 5.22±1.02 mmol/L for TC and from 2.94±0.84 to 2.97±0.74 mmol/L for LDL, although the values remained lower compared to the beginning of the DB phase. HDL continued to increase throughout the ES phase, from 1.38±0.40 to 1.44±0.43 mmol/L (P values not reported). Symptoms scores, SF-36 and QoL-AGHDA scores improved or remained unchanged in patients who previously received somatropin. The symptoms scores for decreased motor ability and/or muscle strength as well as SF-36 and QoL-AGHDA scores improved in patients who previously received placebo (P values not reported). There were a total of 481 adverse events reported in 91.5% of patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most commonly reported adverse events were upper respiratory tract infection, emotion lability, abnormal thinking and psychotic depression. Five serious adverse events were reported, including influenza-like symptoms, convulsions, recurrent craniopharyngioma, recurrent cervical cord tumor and colonic diverticulitis, of which recurrent craniopharyngioma and cervical cord tumor were considered to be related to study treatment. No death occurred during the study. Secondary: Not reported
Gilchrist et al.[105] (2002) GH 0.25 IU/kg/week	OL Patients with GHD that completed the NHP and PGWB during a 12 month DB, RCT	N=61 9 years	Primary: NHP and PGWB scores Secondary: Not reported	Primary: Patients were stratified by continuous treatment during the nine years or discontinuation of treatment after the RCT. At nine years, there was a significant increase in energy and mobility scores of the NHP in the patients that received continuous GH replacement compared to baseline (P=0.04 for both). There were no significant differences compared to baseline in other subsections of the NHP. In patients that discontinued treatment, there were no significant differences compared to baseline in any of the NHP scores. At nine years, there was a significant difference in the change of energy score between the continuous treatment group and discontinuation of treatment group (P=0.008). There were no other significant differences between groups in other NHP scores. At nine years, there was a significant decrease in the general health score of PGWB compared to baseline in patients that discontinued treatment (P=0.03). In patients on continuous treatment, there was a significant increase in vitality score (P=0.003). There were no other significant differences in other scores in either group. When comparing the continuous treatment and discontinued treatment groups, there was a significant difference in change of vitality score (P=0.0004). There were no other significant differences between groups in other scores. Secondary: Not reported
Jørgensen et al.[106] (abstract) (1994)	OL, ES Patients with GHD	N=10 3 years	Primary: Body composition, physical	Primary: An increase in thigh muscle was maintained after three years of GH therapy. There was an increase in body weight and thigh fat volume.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH	on uninterrupted GH therapy for 3 years that completed a previous DB, PC, RCT and 16 month OL trial		performance Secondary; Not reported	Exercise capacity and isometric muscle strength increased significantly compared to the initial placebo period. Secondary: Not reported
Sneppen et al.[107] (2002) Somatropin (Genotropin®) 0.02 IU/kg/day for 4 weeks, followed by somatropin (Genotropin®) 0.03 IU/kg/day vs placebo	DB, PC, RCT Patients 23 to 57 years of age with GHD for a minimum of 2 years with a maximal peak GH response of 3 µg/L with the insulin tolerance test and on stable replacement therapy for other deficient hormones for ≥6 months before trial	N=40 18 months	Primary: Change from baseline in BMD and bone mineral content at 18 months Secondary: Not reported	Primary: There was no significant treatment effect comparing the somatropin and placebo groups after 18 months. The variance of changes was significantly greater in the somatropin treated patients compared to the placebo treated patients for total body BMD (P=0.03), lumbar spine BMD (P=0.001), femoral neck BMD (P=0.01) and femoral trochanter BMD (P=0.04). Secondary: Not reported
Beauregard et al.[108] (2008) Somatropin (Genotropin®) 3 µg/kg/day for patients >50 years of age not receiving oral estrogen; 5 µg/kg/day for patients <50 years of age not receiving oral estrogen; 6 µg/kg/day for patients <50 years of age no receiving oral	DB, PC, RCT Female patients with a history of pituitary and/or hypothalamic disease and GHD	N=43 6 months	Primary: Change from baseline in high-sensitivity CRP, serum lipids, tissue plasminogen activator, soluble E-selectin, insulin resistance and visceral fat mass Secondary: Not reported	Primary: At six months, there was a significantly greater decrease in mean high-sensitivity CRP in the somatropin group compared to the placebo group (38.2±9.6 vs 18.2±6.0%; P=0.03). Patients treated with somatropin had a mean decrease in tissue plasminogen activator of 13.0±4.6% compared to a mean increase of 1.1±5.2% for patients treated with placebo (P=0.02). There was no significant change in soluble E-selectin. Mean TC decreased by 3.1±1.7% with somatropin compared to an increase of 3.8±2.5% with placebo (P=0.04). Mean HDL-C increase by 0.4±2.7% with somatropin compared to a decrease of 10.1±2.1% with placebo (P=0.004). There were no significant differences in the mean change of TG and LDL-C between the groups. At six months, there were no significant changes in fasting glucose, fasting insulin, HOMA, HOMA-β or HbA1c compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
estrogen or had childhood onset GHD regardless of estrogen; doses were increased in all patients depending on IGF-1 levels vs placebo				There was a mean decrease of visceral fat mass of 9.0±5.9% with somatropin compared to an increase of 4.3±2.7% with placebo (P=0.03). Secondary: Not reported
Chihara et al.[109] (2006) Somatropin (Genotropin®) 0.021 mg/kg/week (as 0.003 mg/kg/day) for 4 weeks, followed by 0.042 mg/kg/week for 4 weeks, followed by 0.084 mg/kg/week for remaining 16 weeks vs placebo	DB, PC, RCT Patients 18 to 65 years of age with organic or idiopathic, isolated or multiple, childhood- or adult-onset GHD of ≥2 years	N=75 24 weeks	Primary: Change from baseline in LBM Secondary: Change from baseline in body fat mass, serum lipid profiles, serum IGF-1 and IGFBP-3; symptoms; quality of life; safety	Primary: At 24 weeks, there was a significant increase in LBM in the somatropin-treated patients compared to baseline (4.7%; P<0.05). The increase in LBM with placebo treated patients was not significant (1.0%; P value not reported). When compared to placebo, the increase in LBM was significantly greater with somatropin (P<0.0003). Secondary: At 24 weeks, the body fat mass was significantly decreased in the somatropin group compared to baseline (P<0.05); however, there was a nonsignificant increase with the placebo group. When compared to placebo treated patients the change was significantly different with somatropin-treated patients (-9.3 vs 0.2%; P=0.0004). In the somatropin group, there were significant changes at 24 weeks compared to baseline in TC (-0.3 mmol/L; P<0.05), LDL-C (-0.36 mmol/L; P<0.05), and non-esterified fatty acids (0.1 mEq/L; P<0.05). There were no significant changes in HDL-C, TG or phospholipids. In the placebo group, there were no significant changes in any of the serum lipid profiles. When compared to placebo, only the change in TC was significantly different (P=0.039). At week 24, there was a significant increase in mean serum IGF-1 levels with somatropin-treated patients compared to baseline (P<0.05). The increase in IGF-1 with placebo-treated patients was not significant. The mean change in IGF-1 in the somatropin group was significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than the placebo group (161.9 vs 4.2 µg/L; P<0.0001). The mean change from baseline in IGFBP-3 for the somatropin-treated patients was significantly greater than placebo treated patients (1.0 vs 0.1 mg/mL; P<0.0001). At 24 weeks, all symptoms were reduced from baseline in both treatment groups; however, no statistical analysis was performed. Compared to baseline, quality of life parameters were improved at 24 weeks; though, there were no significant differences between the somatropin and placebo groups. The change in QoL-AGHDA was not significantly different between the groups (P=0.5588). The proportion of patients experiencing adverse events was similar between groups. The most common adverse events associated with somatropin were edema (21.6%), arthralgia (10.8%) and muscle weakness (10.8%). The most common adverse events associated with treatment with placebo were emotional liability (8.3%) and hypertonia (5.6%).
Mauras et al.[110] (2005) Somatropin (Genotropin®) 0.14 mg/kg/week divided in 6 or 7 weekly doses vs placebo	DB, MC, PC, RCT Patients with a diagnosis of childhood-onset GHD treated with GH with an average dose of 0.3 mg/kg/week or 42 µg/kg/day for 3 years prior to study, persistent GHD (defined as peak GH response to insulin tolerance test <5 µg/L), achieved final height and fully pubertal	N=58 24 months	Primary: Effect of somatropin on body composition, BMD, safety Secondary: Effect of somatropin on plasma lipids, IGF-1, carbohydrate metabolism, cardiac function, exercise tolerance and quality of life	Primary: At 24 months, there were no statistically significant differences between somatropin and placebo in change in weight and BMI (P values not reported). At 24 months, there were no significant differences in changes in percent body fat and percent LBM (P=0.448 and P=0.437). There were no significant differences between the groups in spine and whole body BMD at 24 months (-0.29 vs -1.08; P=0.086 and (0.59 vs 0.13; P=0.267, respectively). The rates of reported adverse events were similar between the groups (92% for somatropin and 87% for placebo). Secondary: At 24 months, there were no significant differences in fasting glucose, insulin resistance and insulin sensitivity between the groups (data not reported). Also, there were no significant differences in lipid endpoints between the groups (data not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The median IGF-1 was significantly higher in the somatropin-treated patients compared to the placebo treated patients (326 vs 141 ng/mL; P<0.03). At 24 months, the change in left ventricular systolic function as measured by the shortening fraction was not significantly different between the somatropin and placebo groups (P=0.345). There were no significant differences in LVM at 24 months across the groups. There was no significant difference in IRT at month 24 (P=0.318). The E/A ratio was not significantly different between the groups (P=0.749). At 24 months, the change in mean treadmill exercise tolerance was not significantly different between the groups. The proportion of patients that decreased exercise tolerance was similar between the groups (47% with somatropin vs 38% with placebo). There was no significant difference in the change of quality of life scores between the somatropin and placebo groups at 24 months.
McGauley et al.[111] (1990) Somatropin (Genotropin®) 0.07 IU/kg/day SC vs placebo	DB, PC, RCT Patients 18 to 55 years of age with GHD for at least 12 months	N=24 6 months	Primary: Changes in NHP, PGWB and GHQ scores Secondary: Not reported	Primary: At baseline and one month of study, there was no significant difference in the NHP scores between the somatropin and placebo groups. At six months, patients in the somatropin group had a significantly lower NHP score, indicating a greater improvement in perceived quality of life, compared to those in the placebo group (2.5±1.2 vs 8.2±1.5; P<0.01). Subgroup analysis showed that patients in the somatropin group also had significantly higher perceived energy level compared to patients in the placebo group (2.18±2.2 vs 21.8 ±6.7; P=0.015). With regard to PGWB scores, which assessed self-perceived emotional states, there were no differences between the two groups at baseline, one or six months. Subgroup analysis showed greater improvement in mood with somatropin compared to placebo at six months (14.4±0.4 vs 12.3±0.5; P=0.015). Patients in the somatropin group had a greater reduction in psychological distress, measured by GHQ scores, compared to those in the placebo group at six months (data and P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Cuneo et al.[112] (1993) Somatropin (Genotropin®) 0.07 IU/kg/day SC vs placebo	DB, PC, RCT Patients between 18 and 52 years of age with GHD for at least 12 months	N=24 6 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A-1 and apo B Secondary: Not reported	Primary: Treatment with somatropin was associated with a significant decrease in TC, LDL-C and apo B compared to treatment with placebo. TC decreased 12% from 5.8±0.3 mmol/L at baseline to 5.1±0.3 mmol/L at six months with somatropin and remained at 5.3±0.3 mmol/L throughout the study with placebo (P=0.01). TG increased in the somatropin group from baseline at six months (1.74±0.42 to 1.91±0.41 mmol/L), compared to a decrease from 2.34±0.55 to 1.93±0.47 mmol/L in the placebo group (P>0.05). The changes were not statistically significant when compared to baseline. There was no significant difference between the two groups with regard to changes in HDL. Treatment with somatropin led to a 32% decrease in LDL from 4.22±0.25 to 3.19±0.23 mmol/L at six months, compared to an increase from 3.98±0.33 to 4.25±0.28 mmol/L (P=0.0003). Serum apo B levels decreased by 37% from 1.07±0.06 to 0.84±0.07 g/L with somatropin and increased from 0.96±0.07 to 1.11±0.07 with placebo (P=0.003) Secondary: Not reported
Drake et al.[113] (2003) Somatropin (Genotropin®) 0.35 IU/kg/week or	MC, RCT Adolescent patients with a mean age of 17.0±1.4 years who had childhood-onset GHD and had been receiving GH	N=24 12 months	Primary: Total BMC, lumbar spine BMD, serum bone-specific alkaline phosphatase, IGF-1 Secondary:	Primary: The median percentage increase in total BMC was 3.8% with somatropin and 1.9% with no treatment at six months (P=0.085) and 6.1 and 2.4% with somatropin and no treatment, respectively, at 12 months (P=0.074). When excluding an outlier in the untreated group whose total BMC declined by 25%, the difference in the mean increase in total BMC with somatropin compared to no treatment was 1.7% at six months (95% CI, -0.5 to 4.0; P=0.14) and 2.9% at 12 months (95% CI, 0.1 to 5.7; P=0.043).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
no treatment	treatment with a height velocity of <2 cm/year		Not reported	When compared to baseline, there were no significant changes in the untreated group at six and 12 months (P=0.63 and 0.85; respectively), whereas BMC increased significantly at both six and 12 months compared to baseline (P<0.001 for both). There was no significant difference between the somatropin and untreated groups in the percentage change in lumbar spine BMD at six months (2.3 ad 1.7%; P=0.84) or at 12 months (4.7 and 2.3%; P=0.45). When compared to baseline, patients in the somatropin group led to significant increase in lumbar spine BMD at 12 months (P=0.012) while the increase in the untreated group was nonsignificant (P=0.15). Serum bone-specific alkaline phosphatase was significantly higher in the somatropin group compared to the untreated group at six months (71.0 vs 44.5 IU/L; P=0.019) but not at 12 months (51 vs 44 IU/L; P=0.56). In the somatropin group, there were no significant changes in serum IGF-1 levels throughout the study. In the untreated group, however, serum IGF-1 levels decreased significantly from baseline at six months (P<0.001) with no further significant changes afterwards (data not reported). Secondary: Not reported
Weaver et al.[114] (1995) Somatropin (Genotropin®) 0.125 IU/kg/day for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/day vs placebo	DB, PC, RCT (6 months) followed by OL (6 months Patients with GHD for ≥2 years	N=22 12 months	Primary: Regional fat distribution, metabolic and cardiac risk factors Secondary: Not reported	Primary: Somatropin-treated patients had a significant reduction to total body fat (P<0.01) and percent body fat (P=0.03). There were significant increases in BMI (P<0.01) and body weight (P<0.01) in the somatropin group. There were no significant changes in wait-to-hip ratio and central fat. In the somatropin group, there was a significant reduction in insulin sensitivity (P=0.004) and a significant rises in fasting plasma insulin (P=0.005) and fasting plasma glucose concentrations (P=0.014). There was no change in HbA1c. In the placebo group, plasma glucose had a significant increase (P=0.005), but no other parameters has significant changes. After six months of somatropin treatment for all patients, there were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant reductions in total fat (P=0.01), percent fat (P=0.002), waist-to-hip ratio (P=0.05), central fat (P=0.01), cholesterol (P=0.03) and insulin sensitivity (P=0.0002). There were significant increases in fasting total insulin (P=0.016), specific insulin (P=0.002) and fasting plasma glucose (P=0.001). There were no significant changes in body weight, BMI, HbA1c and TG. Secondary: Not reported
Newman et al.[115] (2011) Somatropin (Humatrope®) 6.25 µg/kg/day for 1 month, followed by somatropin (Humatrope®) 12.5 µg/kg/day vs placebo	DB, RCT (6 months) OL (12 months) Patients 21 to 71 years of age with documented GHD on stable hormonal replacement regimen and able to walk 3 minutes at low speed on a horizontal treadmill	N=30 18 months	Primary: Change from baseline in exercise duration, VO_2max and LVEF at rest and after exercise Secondary: Peak work double product, left ventricular fractional shortening, LVM and wall thickness parameters and echocardio-graphic indices of diastolic function	Primary: At six months, there were no statistically significant differences between somatropin- and placebo-treated patients in exercise duration (P=0.25), VO_2max (P=0.12) and LVEF at rest (P=0.62) and after exercise (P=0.86). There were no significant differences at 18 months in primary cardiac endpoints (P values not reported). Secondary: At six months, there were no statistically significant differences in secondary endpoints between treatment groups (P>0.5). There were no significant differences at 18 months in secondary cardiac endpoints (P values not reported).
Snyder et al.[116] (2007) Somatropin (Humatrope®) 2 µg/kg/day, increased to a maximum of 12 µg/kg/day vs	DB, MC, PC, RCT Patients ≥21 years of age with GHD caused by hypopituitarism, from known pituitary or hypothalamic disease, acquired in adulthood for at	N=67 24 months	Primary: Change from baseline in BMD of lumbar spine at six, 12, 18 and 24 months Secondary: Change from baseline in BMD of hip and total body	Primary: Compared to baseline, there were significant increases in BMD of the spine with the somatropin-treated patients at months 12 (P=0.031), 18 (P=0.014) and 24 (P<0.001). Month 24 was the only time point at which the increase from baseline in BMD of the spine was significantly greater with somatropin compared to placebo (P=0.037). Secondary: At month 24, there was a significant increase from baseline in total hip BMD with somatropin (P<0.05). There were no significant differences in total hip BMD between patients treated with somatropin and placebo at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	least 2 years		composition at six, 12, 18 and 24 months	any time points. There was a significant decrease in trunk fat mass with somatropin compared to placebo at months 12 (P<0.03) and 24 (P<0.03).There were no significant differences between the groups in increase of trunk lean mass.
Chihara et al.[117] (2004) Somatropin (Humatrope®) 0.021 mg/kg/day for 4 weeks, increased stepwise to 0.042 mg/kg/day for 8 weeks then increased to 0.084 mg/kg/day for 12 weeks vs placebo	DB, MC, PC, RCT Patients 18 to 64 years of age with organic or idiopathic, isolated or multiple, childhood- or adult-onset GHD of ≥2 years	N=64 24 weeks	Primary: Change from baseline in body composition, IGF-1, IGFBP-3 and lipid levels; safety Secondary: Not reported	Primary: At 24 weeks, there was a significant increase in LBM with somatropin-treated patients (P<0.001), but a nonsignificant decrease with placebo treated patients. The change in LBM was significantly different comparing somatropin- and placebo-treated patients (4.7±3.9 vs -0.5±4.1%; P<0.001). There was a significant decrease in fat mass compared to a nonsignificant increase with placebo (-9.2±11.8 vs 1.1±6.9%; P<0.001). Serum IGF-1 significantly increased in the somatropin group (P<0.001), while there was a nonsignificant decrease in the placebo group. At 24 weeks, TC significantly decreased with somatropin (P=0.025) and did not significantly change with placebo. The difference between somatropin-treated and placebo-treated patients in change from baseline was significant (-14±34 vs 7±39 mg/dL; P=0.036). The change from baseline in LDL-C was not significant in either group; however, the difference between groups was significant (-7±27 vs 9±27 mg/dL; P=0.04). There were no significant differences in HDL-C and TG. Treatment emergent adverse events of musculoskeletal and connective tissue disorders were reported at a significantly higher rate in the somatropin group compared to the placebo group (P=0.016).There was a nonsignificant higher rate of edema with somatropin compared to placebo. Secondary: Not reported
Chipman et al.[118] (1997) Somatropin (Humatrope®) 6.25	DB, PC, RCT (6 months) OL (12 months)	N=165 18 months	Primary: Safety Secondary: Not reported	Primary: There were no significant differences in discontinuation rates between somatropin and placebo-treat patients with either adult-onset or childhood-onset GHD.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day for 1 month, followed by somatropin (Humatrope®) 12.5 µg/kg/day vs placebo	Patients diagnosed with adult or childhood GHD based on pharmacological stimulation test and on stable treatment with other pituitary controlled hormones			During the DB phase, there were statistically higher incidences of edema and peripheral edema in the adult-onset GHD group treated with somatropin compared to the placebo group (P=0.043 and P=0.017). Somatropin-related adverse events were reported more often in adult-onset patients compared to childhood-set patients. Compared to placebo, adult-onset and childhood-onset patients had significant increases in fasting glucose (P=0.002 and P=0.048). During the 18 months of the trial, 14 serious adverse events were reported with adult-onset patients and three were possibly related to somatropin therapy (carpal tunnel syndrome and lymphoedema). When compared to the DB phase, there was an increase in the incidence of arthralgia, myalgia and paresthesia in the adult-onset patients (statistically analysis not completed). Hypertension was reported in 7.7% of adult-onset patients. There was no hypertension reported in the childhood-onset patients. At six months, there was a significant decrease in mean SBP in childhood-onset patients compared to baseline (P=0.006). There were no significant differences from baseline in SBP at other time points or in other treatment groups. There were no significant changes from baseline in fasting glucose and HbA1c at 18 months in either the adult-onset or childhood onset patients. Secondary: Not reported
Conway et al.[119] (2009) Somatropin (Norditropin®) 0.2 mg/day, increased to 0.6 mg/day at 1 month, increased to 1.0 mg/day at 3 months until end of trial (males) and 0.4 mg/day, increased to 0.9 mg/day at 1	MC, OL, RCT Patients 18 to 25 years of age with BMI 10 to 30 kg/m^2 diagnosed with GHD during childhood and 3 or more pituitary hormone deficiencies or a provocative GH test after their 16th	N=160 24 months	Primary: Change from baseline in BMD at 24 months Secondary: Effect of GH treatment on markers of bone metabolism, IGF-1 and IGFBP-3; safety	Primary: At 24 months, there was a significantly greater increase in lumbar spine BMD with somatropin compared to control (estimated treatment difference, 3.5%; 95% CI, 1.5 to 5.5; P<0.001). The increase in total hip BMD was significantly greater with somatropin compared to control (P=0.05). The change from baseline was not significantly different between the groups for total body BMD (P=0.315). Secondary: At 24 months, the difference in mean alkaline phosphatase levels between somatropin-treated patients and control was statistically significant (estimated treatment difference, 12 IU/L; 95% CI, 2.65 to 21.35; P=0.012). At 24 months, serum IGF-1 levels were significantly higher in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
month, increased to 1.4 mg/day at 3 months until end of trial (females) vs no treatment	birthday			the somatropin group compared to the controls (P<0.0001). Mean IGFBP-3 at 24 months was significantly higher in the somatropin treated patients (P<0.0001). Adverse effects were similar between somatropin and the controls.
Rosenfalck et al.[120] (1999) Somatropin (Norditropin®), dose gradually increased to target of 2 IU/m^2/day vs placebo	DB, PC, RCT Patients with known pituitary pathology and either childhood or adult onset GHD for ≥1 year on adequate substitution of hormonal deficiencies for ≥1 year	N=24 4 months	Primary: Effect of somatropin on body composition, insulin action, non-insulin-mediated glucose uptake and pancreatic β-cell function Secondary: Not reported	Primary: At baseline, patients in the somatropin group had significantly higher body weights compared to patients in the placebo group (P<0.05). At four months, the somatropin-treated patients had significant decreases in body weight (1.6 kg; P<0.05) and fat mass (4.3 kg; P<0.001) and increase in LBM (2.7; P<0.01). There were no significant changes in body composition with placebo treated patients. In placebo-treated patients, there were no significant changes in blood glucose area under the curve after four months. In the somatropin group, fasting blood glucose, insulin, proinsulin and C-peptide significantly increased (P=0.05; P=0.02; P=0.03; P value not reported, respectively). Insulin sensitivity deteriorated significantly in the somatropin-treated patients (P<0.003). The first phase insulin response increased significantly with somatropin-treated patients (P<0.04). There were no significant changes in the placebo-treated patients in insulin sensitivity and first phase insulin response. When compared to placebo, the changes in blood glucose, insulin and insulin sensitivity were significantly different with somatropin (P values not reported). Secondary: Not reported
Burman et al.[121] (1997) Somatropin (Norditropin®) 0.5 U/m^2/day for 2 weeks, followed by	DB, PC, XO Men and women with GHD and adequate replacement of other hormone	N=36 21 months	Primary: Differences by gender in effects of somatropin on IGF-1, body composition, cardiovascular, morbidity and bone	Primary: There were significant increases in IGF-1 levels from baseline in both men and women (P=0.0001 and P=0.0007). The increase was significantly greater in men compared to women (P=0.02). There were significant decreases in percent total body fat in men and women (P=0.0001 and P=0.002). The decrease was significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Norditropin®) 1.0 U/m^2/day for 4 weeks, followed by somatropin (Norditropin®) then 2.0 U/m^2/day for 9 months vs placebo There was a 3 month washout between treatment periods.	deficiencies		metabolism Secondary: Not reported	with men compared to women (7.4±4.1 vs 3.3±3.8%; P=0.002). There were significantly greater decreases in abdominal fat mass and fat mass of the upper extremities in men compared to women (P=0.003 for both). The difference in reduction of fat mass between men and women was not significant (P=0.09). The increase in LBM was significant for each group compared to baseline (P<0.001 for both), but the between group difference was not significant (P value not reported). There was no significant difference in total body weight compared to baseline in either group (P value not significant). There were significant decreases in total serum cholesterol, LDL-C and apo B in men (P=0.008; P=0.03; P=0.0009, respectively). There were no significant changes in these variables in women. Both men and women did not have significant differences in HDL-C and apo A1. There was a significant decrease in LDL/HDL ratio in men (P<0.05), but not women. Men and women had significant increases in Lp(a) compared to baseline (P<0.01 for both). TG was not significantly different from baseline in men or women. The serum activity of plasminogen activator inhibitor 1 decreased significantly compared to baseline in men (P=0.01), but not in women. Serum concentrations of fibrinogen, factor VII and β-thromboglobulin did not differ significantly from baseline in men or women. The serum concentration of osteocalcin, carboxyl-terminal propeptide of type I procollagen level in serum, serum activity of bone-specific alkaline phosphatase, serum level of carboxyl-terminal cross-linked telopeptide of type I collagen in men (P=0.0001; P=0.0001; P=0.0001; P=0.0001, respectively). These variables also increased significantly in women (P=0.001; P=0.0007; P=0.0015; P=0.0007, respectively). There were no significant differences between the groups. Secondary: Not reported
Chihara et al.[122] (2008)	DB, PC, PG, RCT (24 weeks)	N=121 (RCT) N=118	Primary: Change from baseline in mean	Primary: After the 24-week, DB phase, there was a reduction in trunk fat with somatropin and an increase with placebo compared to baseline. The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin (Norditropin®) 0.003 mg/kg/day for 4 weeks, 0.006 mg/kg/day for 4 weeks, 0.012 mg/kg/day for 16 weeks vs placebo After 24 weeks patients entered 48-week, OL trial and received either a fixed dose of 0.003 mg/kg/day for 4 weeks, 0.006 mg/kg/day for 8 weeks, then 0.012 mg/kg/day or an individualized dose based on IGF-1 serum levels and adverse effects with a range of 0.1 mg/kg/day to 1 mg/kg/day.	OL (48 weeks Patients with GHD with appropriate replacement for other hormones for ≥6 months	(OL) 72 weeks	percent trunk fat Secondary: Not reported	difference between somatropin and placebo was statistically significant (difference in mean percent change, -17.82%; 95% CI, -22.90 to -12.74; P<0.0001). The differences in percent total fat mass and percent LBM was significantly greater with somatropin compared to placebo (P<0.0001). After 24 weeks, there were reductions in TC and LDL-C with somatropin, but not placebo. The difference in change from baseline in TC was statistically significant comparing somatropin and placebo (difference in mean change, -16.6 mg/dL; 95% CI, -27.9 to -5.3; P<0.004). The change from baseline in LDL-C was significantly greater with somatropin compared to placebo (P=0.009). There were no significant differences in HDL-C and TG. In the 48-week OL study, the reduction in percent trunk fat compared to baseline was not significantly different with the fixed dose or individualized dose (difference in mean percent change, 1.23%; 95% CI, -7.03 to 9.48; P=0.768). The changes in percent total fat mass and percent LBM were not significantly different comparing the fixed dose and individualized dose groups (P=0.577 and P=0.577). After the 48-week trial, there were no significant between group differences in TC, LDL-C and TG. There was a decrease in HDL-C in the individualized dose group and an increase in the fixed dose group; the between group difference was statistically significant (P=0.002). Secondary: Not reported
Sesmilo et al.[123] (2000) Somatropin (Nutropin®) 10 µg/kg/day	PC, RCT Men 24 to 64 years of age with normal growth and development; benign sellar	N=49 18 months	Primary: Changes in IL-6, CRP, amyloid polypeptide A measurements; anthropomorphic, nutritional and fat	Primary: Compared to placebo, CRP decreased significantly with long-term (months six to 18) somatropin (net difference, -1.9; 95% CI, -3.1 to -0.7; P=0.0027). IL-6 levels also decreased significantly with somatropin compared to placebo (net difference, -1.32; 95% CI, -2.33 to -0.3; P=0.013). There was no significant difference between groups in changes of serum amyloid polypeptide A (net difference, -2.4; 95% CI, -4.8 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	neoplasm, pituitary apoplexy or idiopathic hypopituitarism diagnosed after 18 years of age; peak GH level <5 µg/L after two pharmacologic stimuli		distribution evaluations; IGF-1, glucose, insulin, lipids and HbA1c values Secondary: Not reported	0.06; P=0.056). Changes in weight, BMI, percentage of IBW, waist-to-hip ratio, and nutrient intake did not differ between the somatropin and placebo groups at any time point. With long-term treatment (months six to 18), there was a significant decrease in truncal-to-total fat ratio with somatropin compared to placebo (-0.014±0.004 vs 0.004±0.005; P=0.0087). There was no significant difference in truncal fat-to-extremity ratio between the groups (P=0.052). There was a significant short-term effect (months one and three) with somatropin compared to placebo on lipids. Compared to placebo, there were significant decreases in TC (net difference, -0.86; 95% CI, -1.2 to -0.5; P<0.001), LDL-C (net difference, -0.63; 95% CI, -0.94 to -0.33; P<0.001) and TC-to-HDL-C ratio (net difference, -0.56; 95% CI, -1.1 to -0.03; P<0.040). There were no between group differences in HDL-C or TG. Also, there were no significant differences between groups in long-term effect on lipids. Lp(a) levels increased significantly with long-term somatropin compared to placebo (net difference, 22.0; 95% CI, 5.7 to 38.2; P<0.001). There was a significant increase in glucose, insulin levels and insulin-to-glucose ratios with short-term somatropin compared to placebo (net difference, 0.54; 95% CI, 0.21 to 0.86; P=0.0018, net difference, 37.9; 95% CI, 18.5 to 57.3; P<0.001, net difference, 6.01; 95% CI, 2.28 to 9.74; P=0.0025, respectively). The significant difference was maintained with long-term somatropin compared to placebo for glucose levels (net difference, 0.56; 95% CI, 0.21 to 0.90; P=0.0026), but not insulin levels or insulin-to-glucose ratios. There were no significant differences between groups in HbA1c. Secondary: Not reported
Hoffman et al.[124] (2004) Somatropin 0.0125	DB, MC, PC, RCT Patients 18 to 70 years of age with	N=171 12 months	Primary: Reduction in the proportion of body fat, increase in	Primary: At 12 months, mean body weight and BMI did not significantly change from baseline. In the somatropin group, there were significant decreases in total body and trunk fat and significant increase in total LBM compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/kg/day for 1 month, followed by somatropin 0.025 mg/kg/day as tolerated vs placebo	adult GHD as a result of hypothalamic-pituitary disease acquired ≥18 years of age, no previous therapy with GH and no change in glucocorticoid, thyroid hormone or gonadal hormone replacement therapy within 2 months before study		muscle strength, improved quality of life Secondary: IGF-1 SDS, anthropomorphic measurements, BMD, laboratory evaluations	baseline and the placebo group (P<0.0001). Men experienced a significantly greater reduction of in trunk fat compared to woman (P<0.04). At 12 months, there was no significant change in strength and endurance with somatropin-treated patients. Additionally, there was no significant change in quality of life measurements. Secondary: At 12 months, the mean IGF-1 SDS increased significantly with somatropin-treated patients compared to baseline (P<0.0001). At month 12, there were no significant changes from baseline or between the groups in anthropomorphic measurements. There were no significant changes in BMD for the somatropin-treated or placebo-treated patients. In somatropin-treated patients, there was a significant decrease in LDL-C compared to baseline and placebo-treated patients (P value not reported). LDL-C/HDL-C ratio decreased significantly in somatropin-treated patients (P<0.05).
Thoren et al. (abstract)[125] (1993) GH 0.125 IU/kg/week for 1 month, followed by GH 0.25 IU/kg/week vs placebo	RCT Patients 22 to 65 years of age with pituitary insufficiency	N=20 6 months	Primary: BMD Secondary: Not reported	Primary: At six months, there was no change in the lumbar spine BMD in the GH-treated patients, but there was a significant decrease in the femoral neck BMD (P<0.05). Secondary; Not reported
Chihara et al. (abstract)[126] (2006)	DB, PC, RCT Patients (mean age	N=61 24 weeks	Primary: Change from baseline in trunk fat	Primary: At 24 weeks, there was a -3.4±0.6% change in trunk fat in the GH-treated patients compared to 0.4±0.6% in the placebo treated patients (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 0.012 mg/kg/day vs placebo	37 years) with GHD		Secondary: Not reported	Secondary: Not reported
Salomon et al. (abstract)[127] (1989) GH 0.07 U/kg/day vs placebo	DB, PC, RCT Patients with GHD receiving appropriate thyroid, adrenal and gonadal hormone replacement	N=24 6 months	Primary: Effect of GH on IGF-1, body composition, metabolic rate, cholesterol and TG Secondary: Not reported	Primary: At six months, there was a mean increase of IGF-1 from 0.41±0.05 to 1.53±0.16 in patients treated with GH. There was no effect of GH on body weight. In GH-treated patients, LBM significantly increased (5.5±1.1 kg; P<0.0001) and fat mass significantly decreased (5.7±0.9 kg; P<0.0001), but there were no significant changes in placebo-treated patients after six months. Basal metabolic rate increased significantly at six months compared to baseline in the GH-treated patients (34.4±1.6 kcal/kg of LBM; P<0.001). Fasting plasma cholesterol levels were lower in the GH-treated patients compared to placebo treated patients (P<0.05). TG levels were similar between the groups. Secondary: Not reported
Arwert et al.[128] (2006) GH SC daily at doses adjusted to serum IGF-1 levels normal for age ±5 SD vs placebo	DB, PC, RCT Adults with a mean age of 27.3±6.9 years who had childhood-onset GHD	N=13 6 months	Primary: Changes in scores of the following neuro-psychological tests: POMS depression, anger, fatigue, vigor and tension, digit span forward, digit span backward, associated learning task, associated learning recognition task, number of	Primary: At six months, an improvement in POMS vigor score was seen in patients treated with placebo but not in patients treated with GH (P>0.05). Scores of POMS depression, anger, fatigue and tension improved in both the GH and placebo groups; however, improvement in these scores was not significantly different when comparing GH to placebo. There was no significant difference between the two groups with regard to changes in short-term memory measured by digit span forward, digit span backward and associated learning task scores. In the GH group, the digit span forward score improved slightly from 7.2±1.1 at baseline to 7.8±1.3 at six months and from 6.0±1.0 to 7.1±1.1 in the placebo group (P>0.05). The digit span backward score also improved slightly from 6.4±0.9 at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mistakes on DNMTS task and reaction time on DNMTS task; changes in functional MRI images; IGF-1; IGFBP-3 Secondary: Not reported	baseline to 6.6±1.4 at six months with GH and from 4.9±1.7 to 5.7±1.6 with placebo (P>0.05). The score of associated learning task improved from 22.4±3.4 at baseline to 23.2±3.9 at six months in the GH group but decreased from 19.0±2.9 to 17.6±5.8 in the placebo group (P>0.05). Long term memory, measured by associated learning recognition task, significantly improved with GH compared to placebo. The score of associated learning recognition task improved from 8.4±0.9 at baseline to 9.0±0.0 at six months with GH but decreased from 6.9±2.2 to 5.3±2.2 with placebo (P=0.004). Improvement in verbal recognition memory, measured by DNMTS task, was seen with GH but not with placebo. In the GH group, the number of mistakes on DNMTS task was reduced from 1.2±1.6 at baseline to zero to six months, compared to the placebo group in which the number increased from 1.0+1.3 to 1.1±1.4 (P=0.045). The reaction time on DNMTS task also decreased from 1.5±0.3 to 1.2±0.1 seconds with GH and changed from 1.5±0.4 to 1.5±0.4 seconds with placebo (P=0.055). On functional MRI, decreased activation in the ventrolateral prefrontal cortex was seen in patients receiving GH at six months compared to patients receiving placebo, indicating decreased effort and more efficient recruitment of the neural system. Serum IGF-1 and IGFBP-3 levels both significantly increased at six months in patients receiving GH compared to patients receiving placebo. Serum IGF-1 levels increased from 9.8±4.4 to 30.0±6.6 nmol/L with GH and from 7.6±2.8 to 6.5±2.2 with placebo (P<0.005). Serum IGFBP-3 levels increased from 2.9±0.6 to 4.3±0.7 mg/L with GH and from 2.6±0.5 to 2.7±0.6 mg/L with placebo (P<0.005). Secondary: Not reported
Russell-Jones et al.[129] (1994)	DB, PC, RCT Adult patients with severe GHD	N=18 2 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A1, apo B, Lp(a),	Primary: Compared to placebo, somatropin was associated with significant decrease in TC (P<0.01), LDL-C (P<0.03) and apo B (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 0.018 IU/kg/day SC for 1 month, followed by GH 0.036 IU/kg/day SC for 1 month vs placebo			mevalonic acid, lathosterol, fasting serum insulin and IGF-1 levels Secondary: Not reported	In the somatropin group, TC decreased from 6.44±0.49 mmol/L at baseline to 5.71±0.48 mmol/L at two months, compared to the slight decrease from 5.76±0.35 to 5.57±0.44 mmol/L in the placebo group (P<0.01). A significant reduction in LDL-C from 4.259±0.49 to 3.62±0.44 mmol/L was seen in the somatropin group, compared to a change from 3.62±0.33 to 3.58±0.41 mmol/L in the placebo group (P<0.03). Apo B significantly decreased from 1.30±0.11 to 1.15±0.11 g/L with somatropin compared to a slight decrease from 1.12±0.05 to 1.09±0.06 g/L with placebo (P<0.01). There was a significant reduction in mevalonic acid in the somatropin group compared to the placebo group (P<0.03). Fasting serum insulin and IGF-1 levels increased significantly in the somatropin group compared to the placebo group (P<0.02 and <0.01, respectively). No significant differences were seen in TG, HDL-C, apo A1, Lp(a) and lathosterol between the two groups. Secondary: Not reported
Verhelst et al.[130] (1997) Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week; maximum 4 IU/day vs	DB, ES, MC, OL, PC, RCT Adults patients between 20 and 60 years of age with GHD for at least 24 months and who had not received GH in the previous 12 months	N=148 24 months (DB, PC for 6 months followed by OL for 18 months)	Primary: Changes in body composition, body weight, waist-to-hip ratio, NHP scores, number of sick days, hospitalization rate, IGF-1 levels, safety Secondary: Not reported	Primary: Body composition did not change significantly in the placebo group during the DB phase. After three months of treatment with somatropin, there was significant improvement in body position parameters compared to baseline (P<0.001 for all parameters). The beneficial effects maintained during the first 12 months and declined slightly after 24 months but still remained significantly different compared to baseline. LBM increased from baseline by 2.85±4.63 kg at three months and 2.19±5.14 kg at 24 months. Total body water increased by 1.88±3.53 kg at three months and 1.33±3.84 kg at 24 months. Body fat decreased by 2.51±4.56 kg at three months and 1.48±5.44 kg at 24 months (P<0.001 for all parameters). Total body weight did not change significantly during placebo and somatropin treatment. Waist-to-hip ratio decreased from by 0.01±0.06 at six months (P=0.004) and by 0.02±0.04 at 24 months (P=0.009) compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week; maximum 4 IU/day				to baseline. During the DB phase, patients in the somatropin group reported nonsignificantly greater improvement compared to the placebo group in NHP scores in the following categories: emotions, energy, sleep and social isolation. There was a significantly greater improvement in pain with placebo compared to somatropin (P=0.02). The number of sick days during somatropin treatment decreased from 12.17±3.90 days at baseline to 3.30±2.51 days at 24 months, compared to no change with placebo (P=0.026). The hospitalization rate decreased from 14.9 to 7.7% at 24 months (P=0.12) during somatropin treatment and remained unchanged during the placebo phase. Improvement in physical activity, measured by the percentage of patients sitting most of the time, was also seen with somatropin but not during the placebo phase. There were no changes in the number of physician office visits, civil status and social life activities. No change in serum IGF-1 levels was seen in the placebo group during the DB phase. Serum IGF-1 levels increased significantly after 24 months of treatment with somatropin compared to baseline, from -2.0±2.6 to 1.98±2.40 SDS (P<0.001). More fluid retention-related adverse events were reported in the somatropin group compared to the placebo group during the DB, PC phase (P<0.001). Most commonly reported fluid retention-related adverse events were arthralgia, edema and myalgia. After 24 months of treatment with somatropin, a significant reduction from baseline was seen with SBP (-5.33±15.03 mmHg; P=0.028) but not with DBP. Fasting plasma glucose rose significantly at 24 months by 0.365±0.855 mmol/L compared to baseline (P=0.004). HbA1c was significantly higher compared to baseline at six and 12 months (P=0.002 and 0.02, respectively) but was not significantly from baseline at 24 months. Serum free T_4 decreased significantly compared to baseline after six months of somatropin treatment (P=0.001) and returned to baseline at 24 months. No significant changes were seen with serum free T_3 with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				somatropin treatment. Secondary: Not reported
Hwu et al.[130] (1997) Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 11 months vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months	DB, OL, PC, RCT Patients between 20 and 60 years of age with GHD for at least 2 years and due to pituitary tumor, cranio-pharyngioma, Sheehan's syndrome or idiopathic origins and who had not received GH in the previous 12 months	N=21 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in body composition, lipid profile, IGF-1 levels and insulin sensitivity measured by MIST Secondary: Not reported	Primary: At the end of the DB phase, there was a significant reduction in percent fat (-2.9±2.2%) and fat mass (-1.2±1.0 kg) with somatropin compared to placebo (0.1±1.6 and -0.1±0.8, respectively; P<0.05 for both). Waist-to-hip ratio decreased nonsignificantly by 0.05±0.05 with somatropin compared to placebo (-0.01±0.03). At the end of the OL phase in which both groups received somatropin, there were no differences in body composition between the two groups. There were no differences in lipid profile between the two groups during the PC phase. At the end of the OL phase, HDL in the somatropin group was significantly higher compared to baseline (28±8 vs 38±9 mg/dL; P<0.05). There was a decrease in TC in the placebo group during the PC phase from 215±54 to 179±28 mg/dL and a further decrease to 173±34 mg/dL during the OL phase (P values not reported). In the somatropin group, TC decreased slightly from 195±57 to 192±32 mg/dL in the PC phase and increased to 197±48 mg/dL in the OL phase (P values not reported). TG decreased by 15±61 mg/dL at 12 months in the somatropin group and by 1±58 mg/dL in the placebo group (P values not reported). LDL decreased by 41±59 mg/dL at 12 months in the placebo group and by 5±53 mg/dL in the somatropin group. Compared to baseline, serum IGF-1 levels increased significantly from baseline at 12 months in both the somatropin (58.7±58.8 vs 188.4±115.8 ng/mL; P<0.05) and placebo groups (46.3±29.7 vs 208.1±80.8 ng/mL; P<0.05). Normalization of insulin sensitivity was observed after 12 months of treatment with somatropin. Secondary: Not reported
Webster et al.[132]	DB, ES, OL, PC,	N=18	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(1997) Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months, followed by reinitiating at 0.125 IU/kg/week for 1 month, then 0.25 IU/kg/week for 5 months; maximum 4 IU/day vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months; maximum 4 IU/day	RCT Patients between 18 and 60 years of age with isolated GHD or hypopituitarism for >24 months and who had not received GH in the previous 12 months	12 months (DB, PC for 6 months followed by ES, OL for 6 months)	Changes in lipid profile, Lp(a) and lipoprotein composition Secondary: Changes in BMI, fasting blood glucose, fasting insulin, HbA1c, apo A1 and apo B	During the DB phase, TC decreased from 6.0±0.4 mmol/L at baseline to 5.2±0.4 mmol/L at six months with somatropin; this change did not reach statistical significance when compared to placebo. Changes in all other primary endpoints were not significantly different between the two groups at six months. In patients who received somatropin for 12 months, TC returned to 5.8±0.3 mmol/L at 12 months, which was not significantly different from baseline. Lp(a) decreased from 103 to 52 mg/L at 12 months, but the change did not reach statistical significance. No significant changes were seen in TG. With regard to Lp composition in the somatropin group, there was a transient decrease in the following LDL compositions: TC, free cholesterol, cholesteryl ester, LDL phospholipids and LDL protein at six months compared to baseline (P<0.05); however, these parameters returned to baseline values at 12 months. The composition of HDL, IDL and VLDL did not change significantly throughout the study. Secondary: During the DB phase, fasting plasma glucose increased from 5.0±0.2 mmol/L at baseline to 5.8±0.3 mmol/L at six months in the somatropin group, compared an increase from 4.6±0.2 to 4.9±0.2 mmol/L in the placebo group (P=0.02). Changes in other secondary endpoints were not significantly different between the two groups. In patients who received somatropin for 12 months, fasting blood glucose continued to be elevated compared to baseline at 12 months (5.70±0.18 mmol/L; P=0.036). Fasting insulin was also significantly increased at 12 months compared to baseline (7.8 vs 17.4 mU/L; P=0.044). HbA1c transiently increased at six months from 3.7±0.1% at baseline to 4.0±0.1% (P=0.014) but returned to 3.40±0.13% at 12 months (P>0.05). There were no significant changes in apo A1 and apo B.
Leese et al.[133] (1998) Somatropin	DB, OL, PC, RCT Patients with a mean age of	N=32 12 months (DB, PC for 6	Primary: Changes in lipid profile and Lp(a)	Primary: During the six month DB phase, no significant differences were seen between the two groups with regard to lipid profile and Lp(a). Patients in the somatropin group had significantly lower HDL-C compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months, followed by reinitiating at 0.125 IU/kg/week for 1 month, then 0.25 IU/kg/week for 5 months; maximum 4 IU/day vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months; maximum 4 IU/day	35.1±2.0 years with GHD for at least 24 months and who had not received GH in the previous 12 months	months followed by OL for 6 months)	Secondary: Change in IGF-1 levels	baseline (0.97±0.08 mmol/L) at six months (0.76±0.10 mmol/L; P<0.01) and 12 months (0.75±0.08; P<0.01). In the placebo group, HDL was also lower after somatropin treatment at 12 months (0.59±0.06 mmol/L) compared to baseline (0.92±0.07 mmol/L; P<0.01). TC decreased nonsignificantly from baseline in both groups throughout the study. There were no other notable changes in lipid profile and Lp(a) at 12 months. Secondary: During the six month DB phase, IGF-1 levels increased significantly in the somatropin group compared to the placebo group (37.6±4.1 vs 14.0±2.2 mmol/L; P<0.01). IGF-1 levels in the placebo group also increased at 12 months after somatropin treatment.
Gomez et al.[134] (2000) Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by	DB, ES, OL, RCT Patients with a mean age of 40.3 years with adult-onset GHD for a mean duration of 10.6 years	N=20 24 months (DB, PC for 6 months followed by OL, ES for 18 months)	Primary: Changes in lumbar spine and femoral neck BMD Secondary: Changes in body composition, IGF-1,	Primary: There was a significant increase in both lumbar spine and femoral neck BMD Z-score at 24 months compared to baseline. Lumbar spine BMD Z-score increased from -0.3±1.2 at baseline to 0.41±1.33 at 24 months (P<0.01). Similarly, femoral neck BMD Z-score increased from -0.56±1.44 to 0.1±1.33 at 24 months (P<0.01). Analysis comparing somatropin and placebo was not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Genotropin®) 0.25 IU/kg/week for 23 months vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 17 months			IGFBP-3, calcium, phosphate, creatinine, alkaline phosphatase, PTH and osteocalcin	Twelve months after discontinuation of somatropin, the beneficial effect on lumbar spine and femoral neck BMD was sustained (0.3±1.11 and 0.1±1.1, respectively; P<0.01 for both compared to baseline). Secondary: Compared to baseline, there was a significant increase at 24 months in LBM (44.9±8.9 vs 56.1±9.2 kg; P<0.01) and total body water (32.7±6.5 vs 39.8±6.2 L; P<0.01) as well as a significant decrease in percent body fat (36.2±17.2 vs 20.8±7.9%; P<0.01). A significant increase in serum IGF-1 and IGFBP-3 was seen at 24 months. Osteocalcin transiently increased from 20.1±11.6 to 70.9±96.9 ng/mL at 12 months (P<0.01) and decreased to 38.9±19.3 ng/mL at 24 months (P<0.01). Similarly, serum alkaline phosphatase increased from 1.07±0.32 to 1.46±0.52 µKat/L at 12 months (P<0.01) and declined to close to baseline at 24 months (1.1±0.4 µKat/L; P<0.01). Serum phosphate was also significantly higher at 24 months compared to baseline (1.09±0.14 vs 1.27±0.16 mmol/L; P<0.01). No significant changes were seen in serum calcium, creatinine and PTH.
Holmes et al.[135] (1995) Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 11 months vs placebo for 6 months followed by somatropin	DB, OL, PC, RCT Patients with a mean age of 41.5±2.1 years with adult-onset GHD for at least 2 years and who had never received GH treatment	N=22 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in vertebral trabecular BMD, forearm cortical and integral BMC and BMD and lumbar spine, femoral neck, trochanteric and Ward's triangle integral BMD Secondary: Changes in IGF-1, IGFBP-3, alkaline phosphatase and osteocalcin levels	Primary: At six months, patients receiving somatropin had a significant reduction in forearm cortical BMC (-0.015; P=0.009), forearm cortical BMD (-0.02 g/cm; P=0.005), forearm integral BMD (-0.02 g/cm; P=0.009) and femoral neck BMD (-0.034 g/cm; P=0.048) compared to patients receiving placebo (0.019, 0.003, -0.005 and -0.008 g/cm^2, respectively). In 21 patients who received at least six months of treatment with somatropin in DB and OL phases, there was a significant reduction from baseline by 0.009 g/cm^2 in forearm cortical BMD (P=0.01), by 0.016 g/cm^2 in forearm integral BMD (P=0.03), by 0.022 g/cm^2 in lumbar spine BMD (P=0.003) and by 0.029 in femoral neck BMD (P=0.006). There were no significant changes in other parameters. In 13 patients who received 12 months of treatment with somatropin, lumbar spine BMD decreased from 1.176 g/cm^2 at baseline to 1.143 g/cm^2 at 12 months (P=0.004) while femoral neck BMD increased from 1.000 to 1.015 g/cm^2 (P=0.049). No significant changes were seen in other

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months				parameters. Secondary: After six months of treatment with somatropin, there was a significant increase from baseline in serum IGF-1 (135 vs 360 µg/L; P=0.0001), IGFBP-3 (4.36 vs 4.65 mg/L; P=0.04), alkaline phosphatase levels (67 vs 78 IU/L; P=0.003) and osteocalcin (2.5 vs 4.7 µg/L; P=0.0003).
Chihara et al.[136] (2005) Somatropin (Humatrope®) up to 0.084 mg/kg/week SC daily for 24 weeks (fixed-dose regimen), followed by somatropin (Humatrope®) 0.021 mg/kg/week for 8 weeks, then between 0.021 and 0.084 mg/kg/week for 40 weeks; dose adjusted according to serum IGF-1 levels (individualized-dose regimen) (Group A) vs placebo for 24 weeks followed by somatropin (Humatrope®) 0.021 mg/kg/week SC daily for 8 weeks,	DB, ES, OL, PC, RCT Patients ≥18 years of age with adult-onset or childhood-onset GHD	N=61 (DB, PC) N=59 (ES, OL) 72 weeks (DB, PC for 24 weeks followed by ES, OL for 48 weeks)	Primary: Changes in LBM, fat mass, TC and LDL; safety Secondary: Dose of somatropin and change in serum IGF-1 SDS	Primary: LBM increased by 4.5±5.3 kg after 48 weeks of individualized-dose regimen in Group B (P<0.001 compared to the end of DB phase), which was comparable to the change after 24 weeks of fixed-dose regimen in Group A (4.7±3.9 kg; P value not reported). In Group A, a further increase in LBM by 1.2±4.9 kg was seen when transitioning from fixed-dose to individualized-dose regimens (P value not reported). In Group B, change in fat mass (-10.5±11.6 kg; P<0.001 compared to the end of DB phase) with the 48 week individualized-dose regimen was similar to the change seen with the 24 week fixed-dose regimen in Group A (-9.2±11.8 kg; P value not reported). There was a slight increase in fat mass by 0.3±9.7 kg in Group A after converting from fixed-dose to individualized-dose regimens at 72 weeks (P value not reported). During the individualized-dose regimen in Group B, TC decreased nonsignificantly from 210±42 mg/dL at 24 weeks to 199±38 mg/dL at 72 weeks (P=0.103), whereas LDL-C significantly reduced from 127±34 to 116±38 mg/dL (P=0.032). Data from Group A was not reported. The incidence of edema occurred less frequently with the individualized-dose regimen compared to the fixed-dose regimen in Group A (4 vs 0; P value not reported). The incidence of other adverse events was comparable between the two regimens. In Group B, no significant changes were seen in SBP and DBP, and there was an increase in HbA1c from 4.5±0.6 to 4.7±0.6%. Secondary: The mean somatropin doses in both Group A and B with individualized-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then between 0.021 and 0.084 mg/kg/week for 40 weeks; dose adjusted according to serum IGF-1 levels (individualized-dose regimen) (Group B)				dose regimen (0.050±0.024 and 0.049±0.026 mg/kg/week, respectively) were lower than that with the fixed-dose regimen in Group A (0.078±0.015 mg/kg/week; P value not reported). In Group A, the mean serum IGF-1 SDS at the end of the 24 week fixed-dose regimen was similar to that at the end of 48 week individualized-dose regimen. The number of patients with IGF-1 SDS above normal decreased from six after the fixed-dose regimen to three after the individualized-dose regimen. In Group B, three patients had IGF-1 SDS above normal.
Eden et al.[137] (1993) Somatropin (Humatrope®) 0.5 IU/kg/week SC daily doses for 6 months, followed by placebo for 6 months vs placebo for 6 months followed by somatropin (Humatrope®) 0.5 IU/kg/week SC daily doses for 6 months	DB, RCT, XO Adult patients with adult-onset GHD who had complete pituitary insufficiency for at least 1 year and had never received GH treatment	N=10 12 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A1, apo B, apo E and Lp(a) Secondary: Not reported	Primary: At six weeks of treatment with somatropin, TC significantly decreased from 5.16±1.34 mmol/L at baseline to 4.45±0.75 mmol/L (P<0.05) but increased back to 4.97±1.06 mmol/L at six months of treatment, which was not significantly different from baseline. Similarly, LDL-C was reduced significantly with somatropin at six weeks (2.86±0.61 mmol/L) compared to baseline (3.43±1.09 mmol/L; P<0.05) and increased to 3.26±0.82 mmol/L at six months, which was not significantly different from baseline. TG nonsignificantly decreased from 1.92±1.14 to 1.59±0.48 mmol/L at six months of treatment with somatropin. At six months, HDL-C increased significantly to 0.99±0.34 mmol/L compared to baseline (0.86±0.33 mmol/L; P<0.05). Somatropin was associated with a significant increase in Lp(a) at six weeks (252±152 mg/L; P<0.01) and six months (243±152 mg/L; P<0.01) compared to baseline (137±113 mg/L). There were no significant changes in apo A1, apo B or apo E during the treatment with somatropin. Secondary: Not reported
Elgzyri et al.[138] (2004)	DB, MC, OL, PC, PG, RCT	N=31	Primary: Cardiac function	Primary: No differences between somatropin and placebo were seen in cardiac

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin (Humatrope®) 0.017 mg/kg/week SC daily for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 5 months, followed by somatropin (Humatrope®) 0.017 mg/kg/week for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 11 months vs placebo followed by somatropin (Humatrope®) 0.017 mg/kg/week for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 11 months	Patients between 60 and 79 years of age with adult-onset GHD for 0.5 to 40 years and who had never received GH treatment	18 months (DB, PC for 6 months followed by OL for 12 months)	measured by echo-cardiography, exercise capacity measured by heart rate, BP and maximum work capacity, IGF-1 levels, TC, TG, HDL-C, LDL-C and HDL-C/LDL-C ratio Secondary: Not reported	function during the DB phase. During the OL phase, with regard to the systolic function, the aortic outflow tract integral decreased from 21.8±0.7 cm at baseline to 20.7±0.8 cm at 12 months (P=0.0314) but returned to baseline at 18 months. Similarly, there was a decrease in E-wave from 69±3 to 62±2 cm/second at 12 months (P=0.04) and an increase back to baseline at 18 months. No significant changes were seen in the diastolic function or other parameters on echocardiography. At six months, treatment with somatropin led to a significant increase compared to baseline in heart rate at rest (58 vs 67 bpm; P=0.029), heart rate at maximum work capacity (142 vs 148 bpm; P=0.05) and maximum work capacity (150 vs 160 W; P=0.012). During the OL phase, there was a significant increase in heart rate at rest, heart rate at maximum work capacity and maximum work capacity at 12 months (P=0.017, 0.005 and 0.014, respectively); however, all three parameters returned to baseline at 18 months. No significant changes were seen in SBP and DBP. Serum IGF-1 levels increased significantly in the somatropin group at six months from 6.9 to 18.5 nmol/L (P<0.001). No change was seen in the placebo group during the DB phase but increased from 8.7±0.7 to 18.8±1.6 nmol/L at 18 months (P<0.001). TC was significantly reduced from baseline at six months in both the somatropin (5.7 to 5.2 mmol/L; P=0.013) and placebo groups (5.8 vs 5.5 mmol/L; P=0.02). Similarly, LDL-C decreased significantly from baseline at six months with both somatropin (3.9 to 3.3 mmol/L; P=0.013) and placebo (4.0 to 3.6 mml/L; P=0.014). There were no significant differences in lipid profiles between the two treatment groups at six months. At 18 months, there was a significant reduction in TC from 5.6 to 5.4 mmol/L (P=0.049) and in LDL-C from 3.7 to 3.3 mmol/L (P=0.0008). HDL-C significantly increased from 1.2 to 1.4 mmol/L (P=0.007) whereas there were no significant changes in TG. Secondary: Not reported
Vahl et al.[139] (2000)	DB, OL, PC, PG, RCT	N=19	Primary: Changes in total	Primary: Total body fat increased at 12 months (22.68±2.67 kg) compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin (Norditropin®) 2 to 5 IU daily for 12 months (DB), followed by somatropin (Norditropin®) 2 IU daily for 12 months (OL) vs placebo for 12 months (DB), followed by somatropin (Norditropin®) 2 IU daily for 12 months (OL)	Adult patients with a mean age of 20.20±0.65 years who had childhood-onset GHD and had been receiving GH treatment for at least 3 years	24 months (DB, PC for 12 months followed by OL for 12 months)	body fat, subcutaneous abdominal fat, intra-abdominal fat, muscle and fat of the thigh, LBM, waist-to-hip ratio, isometric quadriceps muscle strength, exercise capacity, GHQ score, IGF-1, IGFBP-1 and IGFBP-3 levels; lipid profile; fasting glucose; serum insulin levels; HbA1c; total T_4 and T_3 and free T_4 and T_3 levels Secondary: Not reported	baseline in the placebo group (26.49±2.51 kg; P=0.01) and subsequently decreased after somatropin treatment at 24 months (21.02±2.57 kg; P=0.065 compared to 12 months). The increase in total body fat at 12 months in the placebo group was significantly greater compared to the somatropin group (P=0.04). No significant changes were seen in the somatropin group throughout the study (data not reported). Subcutaneous abdominal fat mass increased from 253.71±31.46 cm^2/10 mm at baseline to 318.05±22.69 cm^2/10 mm at 12 months (P=0.04) and decreased at 24 months in the placebo group (299.59±34.92 cm^2/10 mm; P=0.4). Similarly, compared to baseline, intra-abdominal fat mass slightly increased after 12 months (84.41±20.86 vs 95.66±11.74 cm^2/10 mm; P=0.13) and decreased at 24 months in the placebo group (82.27±15.60 cm^2/10 mm; P=0.13). No significant changes were seen in the somatropin group with regard to subcutaneous abdominal fat and intra-abdominal fat. Muscle mass of the thigh in patients receiving placebo decreased from 121.3±11.2 cm^2/10 mm at baseline to 118.2±11.7 cm^2/10 mm at 12 months (P=0.12) and increased to 130.0±10.9 cm^2/10 mm at 24 months (P=0.002). An opposite trend in fat mass of the thigh was observed with the endpoint being 84.1±9.7, 104.9±13.6 and 98.9±16.1 cm^2/10 mm at baseline, 12 months (P=0.007) and 24 months (P=0.3), respectively. No significant changes were seen in the somatropin group. In the placebo group, LBM remained unchanged at 12 months (50.85±5.88 kg) compared to baseline (52.36±4.86 kg; P=0.12) but increased with somatropin treatment at 24 months (60.70±5.59 kg; P=0.006). No significant changes were seen in the somatropin group. The waist-to-hip ratio in the placebo group decreased slightly from 0.931±0.06 at baseline to 0.877±0.03 at 12 months (P=0.6) and decreased slightly further with somatropin treatment at 24 months (0.837±0.03; P=0.12). No significant changes were seen in the somatropin group. Isometric quadriceps muscle strength and exercise capacity, measured bicycle ergometer, did not change significantly throughout the study with both somatropin and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				With regard to the GHQ scores, there was a slight increase from baseline at 12 months in the placebo group (45.1±4.7 vs 50.5±6.9; P=0.5) and a decrease at 24 months (38.3±3.5; P=0.07), indicating improvement in perceived quality of life after resuming somatropin treatment. There were no significant changes in the somatropin group. In the placebo group, IGF-1 and IGFBP-3 levels decreased significantly from baseline at 12 months (P<0.002) and increased significantly at 24 months with somatropin (P<0.02). IGFBP-1 decreased significantly from 12 months to 24 months (P=0.04). The change in IGF-1 levels at 12 months was significantly different between somatropin and placebo (P=0.003). No significant changes were seen with regard to TC in both the somatropin and placebo groups. In the somatropin group, HDL-C remained unchanged from baseline to 12 months (1.27±0.14 vs 1.29±0.30 mmol/L; P value not reported) but increased significantly at 24 months compared to 12 months (1.39±0.27 mmol/L; P<0.05). HDL-C in the placebo group did not change significantly during the study. In patients receiving somatropin, there was a gradual but nonsignificant decrease of LDL-C throughout the study while TG remained unchanged. In the placebo group, there was a slight but nonsignificant increase from 12 months at 24 months with LDL-C and TG. In the placebo group, fasting glucose decreased from baseline at 12 months (5.1±0.2 vs 4.9±0.2 mmol/L; P=0.05) and increased again at 24 months after treatment with somatropin (5.3±0.2 mmol/L; P=0.03). No significant changes were seen in the somatropin group. Similarly, serum insulin levels decreased from baseline at 12 months in the placebo group (100.3±19.9 vs 64.9±8.6 pmol/L; P=0.08) and increased at 24 months (131.6±46.0 pmol/L; P=0.16). In the somatropin group, serum insulin levels increased gradually throughout 24 months (46.4±6.2,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				57.1±14.1 and 66.4±14.2 pmol/L at baseline, 12 months and 24 months; P>0.05 for both). The change at 12 months was significantly different between placebo and somatropin (P=0.04). HbA1c remained unchanged after 12 months of treatment with placebo (P=0.6) but increased at 24 months after resuming somatropin (P=0.07). No significant changes were seen in the somatropin group. Total T_3 did not change significantly with either somatropin or placebo. Total T_4 increased significantly in the placebo group at 12 months (166.0±11.3 nmol/L) compared to baseline (149.0±10.5 nmol/L; P=0.03) and decreased at 24 months after somatropin treatment (150.0±11.7 nmol/L; P=0.09). No significant changes were seen with somatropin. Free T_3 decreased from baseline at 12 months in the placebo group (5.6±0.4 vs 5.0±0.4 pmol/L; P=0.02) and increased slightly at 24 months (5.2±0.6 pmol/L; P=0.8). No significant changes were seen in the somatropin group. Free T_4 remained unchanged at 12 months compared to baseline and decreased from 23.8±2.6 pmol/L to 19.3±1.6 pmol/L in the placebo group (P value not reported). In the somatropin group, free T_4 decreased from 17.1±3.1 pmol/L at 12 months to 14.9±2.7 pmol/L at 24 months (P value not reported). Secondary: Not reported
Nolte et al.[140] (1997) Somatropin (Norditropin®) with a target dose of 2 IU/m^2/day for 24 months	DB, MC, PC, RCT Patients between 18 and 60 years of age with adult-onset GHD due to a known cause and who had never received GH	N=38 24 months (DB, PC for 12 months followed by OL for 12 months)	Primary: Changes in lipid profile and Lp(a) Secondary: Changes in BMI and waist-to-hip ratio	Primary: Compared to baseline, there was a significant reduction in LDL-C (191 vs 151 mg/dL; P<0.001), TC (269 vs 226 mg/dL; P<0.001) and TG (214 vs 144 mg/dL; P<0.05) at 24 months in the somatropin group. There were no significant changes in these three parameters in the placebo group during both DB and OL phases. No significant changes were seen in HDL-C throughout the study in both treatment groups. Changes in lipid profile were not compared between the two treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo for 12 months followed by somatropin (Norditropin®) with a target dose of 2 IU/m^2/day for 24 months	treatment			Lp(a) increased significantly at 24 months compared to baseline in both the somatropin (6.7 vs 10.6 mg/dL; P<0.001) and placebo groups (9.5 vs 11.8 mg/dL; P<0.05). Secondary: The BMI and waist-to-hip ratio did not change significantly throughout the study in both treatment groups.
Bell et al.[141] (2004) GH 0.125 IU/kg/week daily for 4 weeks, followed by GH 0.25 IU/kg/week daily vs placebo for 6 months, followed by GH 0.125 IU/kg/week daily for 4 weeks, followed by 0.25 IU/kg/week daily	DB, OL, PC, PG, RCT Patients between 21 and 60 years of age with GHD and who had not received GH in the previous 2 years	N=51 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in waist and hip circumference, waist-to-hip ratio, BMI, conicity index, absolute trunk fat, somatotype, TC, TG, HDL-C, LDL-C, HDL-C/LDL-C ratio, SBP, DBP and pulse pressure Secondary: Not reported	Primary: In both male and female patients, treatment with placebo during the first six months led to a slight increase in waist and hip circumference, absolute trunk fat and conicity index, whereas an increase in these parameters was observed after initiation of GH both in the GH group throughout the study and in the placebo group during six to 12 months. No notable or consistent trends were seen with other body composition parameters, lipid profile, BP and pulse pressure. In the 27 male patients, significant differences were observed between the GH and placebo groups at six months with regard to changes in waist circumference (-2.4 vs 1.08 cm; P=0.0001), absolute trunk fat (-2.4 vs 0.26 kg; P=0.0001), conicity index (-0.02 vs 0.01 units; P=0.0001) and somatotypes (P=0.001). The significance of differences in other parameters was not reported. In the 24 female patients, reduction in absolute trunk fat was significantly different between the GH and placebo groups at six months (-2.3 vs -0.1 kg; P=0.033). The significance of differences in other parameters was not reported. Secondary: Not reported
Colao et al.[142] (2005) GH 3 to 4 µg/kg/day adjusted up to 50	RCT, XO Patients 25 to 50 years of age diagnosed with	N=34 12 months	Primary: Change from baseline in cardiovascular risk factors and IMT	Primary: After the first six months in the patients in Group A, there were significant increases in IGF-1 (P<0.01) and HDL-C (P<0.01) and decreases in DBP (P<0.01), TC/HDL-C ratio (P<0.01) and CRP (P<0.01). At 12 months, the patients in Group A had a significant decrease in IGF-1 level (P<0.05) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
percentile of normal IGF-1 for age and sex for 6 months then no treatment for 6 months (Group A) vs no treatment for 6 months then GH 3 to 4 µg/kg/day adjusted up to 50 percentile of normal IGF-1 for age and sex for 6 months (Group B)	GHD and partial or complete hypopituitarism		Secondary; Not reported	significant increases in TC/HDL-C ratio (P<0.05) and CRP (P<0.01). At 12 months, the mean IMT was significantly lower compared to baseline (P=0.0003). After the first six months, there were no significant differences in any of the parameters in the patients of Group B. At 12 months, the patients of Group B had significant increases in IGF-1 level (P<0.01) and HDL-C (P<0.05) and significant decreases in DBP (P<0.01), TC (P<0.05), TC/HDL-C ratio (P<0.01) and CRP (P<0.01). At 12 months, the mean IMT was significantly lower compared to baseline (P=0.003). Secondary: Not reported
Underwood et al.[143] (2003) Somatropin (Nutropin®) 25 µg/kg/day (0.175 mg/kg/week) SC daily (high-dose group) vs somatropin (Nutropin®) 12.5 µg/kg/day (0.085 mg/kg/week) SC daily (low-dose group) vs placebo	DB, MC, PC, RTC Patients <35 years of age with childhood-onset GHD who had completed pediatric GH treatment, had reached adult height and had not received GH in the previous 12 months	N=64 24 months	Primary: Changes in total body fat, trunk fat mass, LBM, lumbar spine BMD, total body BMD, sum of skinfold thickness, lipid profile, cardiac function and quality of life Secondary: Changes in IGF-1 SDS, alkaline phosphatase, glucose metabolism, and other laboratory parameters; safety	Primary: At 24 months, there was an increase in total body fat in the placebo group (2.3±3.4 kg) and a dose-dependent decrease in the two somatropin groups (-0.7±4.8 and -3.7±3.6 kg in low- and high-dose groups, respectively; P value not reported). Similarly, the mean change in trunk fat was 2.6±5.1, -3.8±6.6 and -7.7±5.6 kg in the placebo, low- and high-dose groups, respectively (P<0.0001). Only high-dose somatropin led to a significant decrease in trunk fat compared to baseline (P=0.0011). LBM increased from baseline by 3.1±5.7% with placebo, 13.4±8.4% with low-dose somatropin and 13.4±10.2% with high-dose somatropin (P value not reported). At 24 months, the mean change from baseline in lumbar spine BMD Z-score was 0.09±0.27 with placebo (P=0.28 compared to baseline), 0.29±0.28 with low-dose somatropin (P=0.013) and 0.41±0.42 with high-dose somatropin (P=0.0034), showing a dose-dependent effect (P=0.032). A dose-dependent increase in total body BMD was also seen; however, the change was not statistically significant in the active treatment groups when compared to baseline. The sum of skinfold thickness decreased from 99.5 mm at baseline to 87.1

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mm at 24 months with high-dose somatropin (P<0.05) and from 97.3 to 91.2 mm with low-dose somatropin (P<0.05) while there was no significant change with placebo. At 12 months high-dose somatropin led to a significant reduction from baseline in LDL-C and LDL-C/HDL-C ratio (P<0.04 for both). No significant changes were seen in the other groups. There was a dose-dependent response for LDL-C/HDL-C ratio across the three groups at six and 12 months (P=0.006) but not at 24 months. Echocardiography showed no significant change in IVS, LVPW, LVEDD, LVESD and fractional shortening. There was a significant increase in mean LVM at 24 months with high-dose somatropin (P=0.01) but not with low-dose somatropin or placebo. There were no significant differences across the three treatment groups with regard to quality of life measured by the Index of General Well-Being, Beck Depression Index, STAI and Rathus Assertiveness Test. Secondary: There was a dose-dependent increase in serum IGF-1 SDS (P=0.0001) and serum alkaline phosphatase (P≤0.0006) at 24 months. An increase in fasting serum glucose from 79±8 mg/dL at baseline to 90±13 mg/dL at 24 months was seen in the low-dose somatropin group (P<0.03) and an increase from 85±7 to 90±11 mg/dL was seen in the high-dose somatropin group (P<0.03). Fasting serum insulin also increased from 9 to 10 mU/L with low-dose somatropin and from 10 to 14 mU/L with high-dose somatropin (P<0.03 for both). No significant changes were seen in postprandial glucose and insulin or in HbA1c. No significant changes were seen in electrolytes, renal, liver or thyroid functions. Similar numbers of adverse events were reported in the three groups, including edema and arthralgia.
Yuen et al.[144] (2005)	OL, RCT Adult patients with	N=33 12 months	Primary: Change in whole-body insulin	Primary: At 12 months, insulin sensitivity improved with the low-dose regimen (1.3±0.4 mg/kg/minute) compared to the standard-dose regimen (-0.3±0.7

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Somatropin (Genotropin®) 0.1 mg/day SC (low-dose group) vs somatropin (Genotropin®) 0.2 mg/day SC, titrated to serum IGF-1 SDS of 0 (standard-dose group) vs no treatment	severe adult-onset or childhood-onset GHD and who had not received GH in the previous 12 months		sensitivity index (M-value) and fasting blood glucose Secondary: Change in truncal fat, truncal LBM, lipid profile, nonesterified fatty acid, CRP, IL-6, TNF-α and adiponectin	mg/kg/minute; P<0.05) and to no treatment (-0.3±0.4 mg/kg/minute; P<0.02). There was a decrease in fasting blood glucose in the low dose group (-0.4±0.1 mmol/L) compared to a slight increase in the standard-dose and untreated groups (0.1±0.1 mmol/L for both; P<0.01 for both). Secondary: Treatment with both low- and standard -dose regimens led to similar reduction in truncal fat mass (-1.57±0.43 and -0.70±0.58 kg; P>0.05). There were no significant differences across all three groups with regard to changes in truncal LBM (-0.30±0.29, 0.23±0.32 and 0.00±0.38 kg for low-dose, standard-dose and no treatment, respectively). No significant differences were seen in TC, TG, HDL-C and LDL-C across the three groups. Compared to the low-dose regimen, the standard-dose regimen led to greater increase in fasting nonesterified fatty acid (455±167 vs 34±113 µmol/L; P<0.05) and greater reduction in IL-6 (-2.5±0.8 vs -1.2±1.1 ng/L; P<0.05). No significant changes were seen between the two somatropin groups in CRP, TNF-α and adiponectin.
Chihara et al.[145] (2010) GH (Growject®*) 0.003 mg/kg/day for 4 weeks, followed by GH 0.006 mg/kg/day for 8 weeks, followed by GH 0.0012 mg/kg/day for the last 12 weeks (high dose) vs	DB, PC, RCT (24 weeks) OL (48 weeks) Patients 18 to 64 years of age with idiopathic or organic, isolated or combined with other deficiencies, sever adult GHD and stable replacement of other hormone deficiencies for ≥3 months	N=96 72 weeks	Primary: Dose relationship of GH replacement on body composition, IGF-1 and serum lipids Secondary: Not reported	Primary: After 24 weeks, there were significant increases in IGF-1 SDS for the high dose and low dose groups compared to baseline (P<0.001 for both), but no significant change with the placebo group. Compared to placebo, there were significant changes in IGF-1 SDS (P<0.001). The changes in IGF-1 SDS were significant greater with the high dose group compared to the low dose group (P value not reported). After 24 weeks, there were significant decreases in percent trunk mass and percent total fat mass in the high dose and low dose groups (P<0.001 for all), but not the placebo group. There was a significant increase in percent LBM for the high dose and low dose group (P<0.001), but not the placebo group. The changes in body composition for the high dose and low dose groups were significant compared to the placebo group (P<0.001). The changes in body composition were significantly greater in the high dose

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Growject®*) 0.003 mg/kg/day for 4 weeks, followed by GH 0.006 mg/kg/day for 8 weeks, followed by GH 0.006 mg/kg/day for the last 12 weeks (low dose) vs placebo In the OL phase doses were adjusted to a range of 0.003 mg/kg/day to 0.012 mg/kg/day according to IGF-1 level.				group compared to the low dose group (P values not reported). At 24 weeks, TC decreased significantly compared to baseline in the high dose and low dose groups (P<0.001 and P<0.05), but not the placebo group. LDL-C decreased significantly in the high dose group (P<0.001). There was a nonsignificant decrease in LDL-C with the low dose group and a nonsignificant increase in the placebo group. The changes in TC and LDL-C were not significant differences between the high dose and low dose groups. There were no significant changes in TG with any of the groups. There was a significant dose-responsiveness in the three groups (P<0.001). In the OL phase, there were significant changes at 72 weeks compared to baseline in percent trunk fat mass, percent LBM, percent total fat mass, IGF-1 SDS, TC and LDL-C (P<0.001). There were no significant differences in adverse events between the three groups during the 24-week DB phase. There were no clinically relevant adverse reactions during the 48-week OL phase. Secondary: Not reported
Attanasio et al.[146] (2004) Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH in the previous 6 weeks and had a height velocity <1 cm/year	N=149 2 years	Primary: Changes in LBM, fat mass and lipid profile Secondary: Not reported	Primary: LBM increased significantly from baseline at two years in both the pediatric and adult dose groups compared to the untreated group (5.2±4.4 and 5.1±3.9 vs 1.0±3.0 kg; P<0.001 for both dose regimens combined compared to no treatment). There was no significant difference between the two dose groups. At two years, there was a decrease from baseline in fat mass in both the pediatric and adult dose groups compared to an increase in the untreated group (1.1±4.0 and -1.6±5.8 vs 1.5±5.3 kg; P=0.029). There was no significant difference between the two dose groups. There were no significant differences at two years with regard to changes in TC among the three treatment groups (-1.2±38.7, 5.2±38.3 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day (0.09 mg/kg/week) (adult dose group) vs no treatment				15.0±29.2 mg/dL with pediatric dose, adult dose and untreated groups, respectively; P=0.172). The LDL-C/HDL-C ratio was significantly decreased in the pediatric dose group and remained unchanged in the adult dose group, compared to an increase in the untreated group (-0.09±0.80 and 0.00±0.90 vs 0.39±0.90; P=0.05). There was no significant difference between the two dose groups. Secondary: Not reported
Shalet et al.[147] (2003) Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5 µg/kg/day (0.09 mg/kg/week) (adult dose group) vs no treatment	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH in the previous 6 weeks and had a height velocity <1 cm/year	N=149 2 years	Primary: Changes in total BMC, total BMD, lumbar spine BMD and hip BMC Secondary: Changes in serum bone-specific alkaline phosphatase levels and urinary ICTP-to-creatinine ratio; safety	Primary: At two years, a significant percentage increase was seen with regard to total BMC (5.6±8.3%; P<0.001) and total BMD (2.9±5.8; P=0.003) in the untreated group when compared to baseline. In the pediatric and adult dose groups, the increase in total BMC (8.1±7.6 and 9.5±8.4%, respectively; P=0.008 for both dose groups combined compared to the untreated group) and total BMD (3.2±4.5 and 4.7±4.5%, respectively; P=0.019) was significant greater compared to the untreated group. There was no significant difference between the two dose groups. Compared to no treatment, pediatric and adult dose regimens at two years was associated with greater increase in lumbar spine BMC (7.6±8.7 and 10.0±11.2 vs 4.1±6.7%; P=0.013) and BMD (5.1±7.1 and 6.1±7.4 vs 3.1±4.4%; P=0.027). There were no significant changes at the hip and femoral neck BMD, and there was no difference between the two dose groups. Secondary: At two years, serum bone-specific alkaline phosphatase increased significantly from baseline in both the pediatric and adult dose groups compared to a decrease in the untreated group (5.12±16.55 and 7.86±13.27 vs -0.29±9.74 IU/L; P=0.013). Similarly, urinary ICTP-to-creatinine ratio increased in the pediatric and adult dose groups compared to the untreated group (327±1019 and 24±684 vs -265±609; P=0.004). There was no significant difference between the two dose groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Three clinically relevant serious adverse events were reported, including one case of obstructive sleep apnea in the untreated group, one recurrence of optic glioma in the adult dose group and one osteolytic lesion in a patient with Langerhans cell histiocytosis in the adult dose group.
Attanasio et al.[148] (2005) Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5 µg/kg/day (0.09 mg/kg/week) (adult dose group) vs no treatment	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH in the previous 6 weeks and had a height velocity <1 cm/year	N=66 2 years	Primary: Change in quality of life measured by QLS-H score Secondary: Not reported	Primary: There were no significant differences between the pediatric and adult dose groups with regard to the change in total QLS-H score at two years. When data from the two somatropin groups were combined, there was no significant change in total QLS-H score (0.12±0.89) compared to the no treatment group (0.0±0.8; P=0.385). When looking at individual components of QLS-H, treatment with somatropin was associated with a significant improvement from baseline in body shape (0.46±1.26; P=0.035) and the ability to become sexually aroused (0.23±0.78; P=0.038); however, the improvement was not significant when compared to no treatment (-0.12±0.78; P=0.106, 0.06±0.72; P=0.368, respectively). There were no significant changes between somatropin and no treatment with regard to the ability to tolerate noise, ability to tolerate stress, concentration, ability to cope with own anger, initiative, physical endurance and self-confidence. Secondary: Not reported
Abrahamsen et al.[149] (2004) Somatropin (Norditropin®) 2 IU/m^2/day (14 µg/kg/day) SC (high-dose group) vs somatropin	DB, PC, RCT Patients ≥18 years of age with adult-onset GHD for at least 1 year and who had never received GH treatment	N=58 12 months	Primary: Changes in body composition and lipid profile Secondary: Change in IGF-1 levels	Primary: At 12 months, the median reduction in fat mass was 0.5 kg with placebo, 1.5 kg with low-dose somatropin, 1.8 kg with medium-dose somatropin and 4.7 kg with high-dose somatropin, demonstrating dose-dependent effect with multiple regression analysis (P<0.001). Subanalysis further showed that the reductions in fat mass of the trunk and the extremities were also dose-dependent (P<0.001 and <0.05, respectively). There was a median increase in LBM by 0.7 kg with placebo, 3.2 kg with low-dose somatropin, 2.5 kg with median-dose somatropin and 2.4 kg with high-dose somatropin. Multiple regression analysis showed no dose-dependent correlation (P=0.97). Subanalysis showed that the increase in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Norditropin®) 1.5 IU/m^2/day (9 µg/kg/day) SC (medium-dose group) vs somatropin (Norditropin®) 0.5 IU/m^2/day (4 µg/kg/day) SC (low-dose group) vs placebo				LBM was sex-dependent, with a median increase by 4.1 kg in men and 0.6 kg in women (P<0.001). When data from all three active treatment groups were combined, there was a significant change from baseline at 12 months in TC (6.3%; P<0.01) and LDL-C (10.8%; P<0.001) but not in TG or HDL-C. A somatropin dose-dependent effect was seen in the reduction of TC (P<0.01) and LDL-C (P<0.001). In the low dose group, no significant changes were seen in lipid profile. Medium-dose somatropin was associated with a significantly lower LDL-C, whereas high-dose somatropin led to a significant decrease in both LDL-C and TC. Secondary: A dose-dependent increase in serum IGF-1 levels was seen, with the mean change being 8, 161, 239 and 412% in the placebo, low-, medium- and high-dose groups, respectively (P<0.001).
Abrahamsen et al.[150] (2002) Somatropin (Norditropin®) 2 IU/m^2/day (14 µg/kg/day) SC (high-dose group) vs somatropin (Norditropin®) 1.5 IU/m^2/day (9 µg/kg/day) SC (medium-dose group) vs	DB, PC, RCT Patients ≥18 years of age with adult-onset GHD for at least 1 year and who had never received GH replacement	N=58 12 months	Primary: Changes in lumbar spine, femur, forearm and whole body BMD Secondary: Changes in serum alkaline phosphatase, ICTP, PICP and PIIINP levels	Primary: Lumbar spine BMD decreased by 2.48±1.09 with placebo and increased by 2.43±1.94 and 3.10±1.45% with low- and medium-dose somatropin, respectively, compared to a decrease of 0.24±1.54 with high-dose somatropin (P<0.05 for intergroup differences). Similarly, there was a decrease in proximal forearm and whole body BMD with high-dose somatropin (-1.90±0.99 and -2.29±0.60%, respectively) when there was an increase at these sites with both low- and medium-dose somatropin (P<0.05 for both). Similar trend was seen in femoral shaft and total femur BMD, though the intergroup differences were not significant. With regard to ultradistal forearm BMD, there was a decrease with both medium- and high-dose somatropin (-1.09±0.83 and -4.92±1.43%, respectively) compared to an increase with low-dose somatropin and placebo (0.92±1.36 and 0.52±0.59, respectively; P<0.01). Secondary: There were no significant changes in bone turnover markers with placebo throughout the study. Serum alkaline phosphatase increased significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Norditropin®) 0.5 IU/m^2/day (4 µg/kg/day) SC (low-dose group) vs placebo				in all three somatropin groups and returned to baseline at 12 months in the low dose group only. ICTP, PICP and PIIINP levels also increased significantly and remained elevated throughout the study in all three somatropin groups.
Kehely et al.[151] (2002) Somatropin (Humatrope®) 3 µg/kg/day for 3 months, followed by somatropin (Humatrope®) 6 µg/kg/day for 3 months (low-dose group) vs somatropin (Humatrope®) 6 µg/kg/day for 3 months, followed by somatropin (Humatrope®) 12 µg/kg/day for 3 months (standard-dose group)	MC Adult patients with childhood- or adult-onset GHD who had not received GH in the previous 6 months	N=595 6 months	Primary: Changes in LBM and fat mass Secondary: Changes in serum IGF-1 and IGFBP-3 SDS; safety	Primary: At six months, patients in the low-dose group gained 1.81 kg of LBM, compared to 2.33 kg for patients in the standard-dose group (P=0.141). The changes in both groups were significant compared to baseline. Patients in the standard-dose group had greater reduction in fat mass compared to those in the low-dose group after six months of treatment (-2.14 vs -1.54 kg; P=0.006). The changes in both groups were significant compared to baseline. Secondary: Serum IGF-1 and IGFBP-3 SDS increased significantly from baseline at six months in both treatment groups. The increase in IGF-1 SDS with the standard-dose group was greater than the low-dose group (P=0.024). There were no significant differences between the two groups with regard to IGFBP-3 SDS (P=0.454). Overall, fewer patients in the low-dose group reported at least one adverse event compared to the standard-dose group (56.0 vs 66.2%; P=0.01). The dose-dependent difference was significant in patients with adult-onset GHD (P=0.008) but not in patients with childhood-onset GHD (P=0.423). The most commonly reported adverse events were arthralgia, headache and peripheral edema.
Rahim et al.[152] (1998) GH 0.125	OL Patients with adult onset GHD for at	N=15 3 years	Primary: Change from baseline in BMD at three years for	Primary: In Group A at three years, the lumbar spine BMD and trochanter BMD increased significantly from baseline (3.7%; P=0.028 and 4.0%; P=0.046, respectively). There was a nonsignificant decrease in femoral neck BMD

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IU/kg/week for 4 weeks, followed by GH 0.25 IU/kg/week; up to a maximum of 4 IU/day for 3 years (Group A) vs GH 0.125 IU/kg/week for 4 weeks, followed by GH 0.25 IU/kg/week; up to a maximum of 4 IU/day for 6 to 12 months (Group B)	least 2 years that completed a previous RCT and had not received GH prior to the study		Group A and two years after completion of GH treatment for Group B Secondary: Not reported	(1.9%; P=0.39). Ward's area BMD decreased by 6.5% at three years (P=0.09). Forearm cortical BMD decreased by 2.6% (P=0.18). Two years after completion of GH therapy in Group B, trochanter BMD significantly increased by 5.9% (P=0.049). There were no significant differences from baseline in lumbar spine BMD (P=0.67), Ward's area BMD (P=0.57), femoral neck BMD (P=0.86) and forearm cortical BMD (P=0.31). Secondary: Not reported
Hoffman et al.[153] (2004) Somatropin (Humatrope®) 4 µg/kg/day for 4 months, followed by somatropin (Humatrope®) 8 µg/kg/day for 2 months, followed by somatropin (Humatrope®) 12 µg/kg/day for 2 months (fixed-dose group) vs	MC, OL, PG, RCT Patients ≥20 years of age with adult- or childhood-onset GHD and who had not received GH in the previous 12 months	N=387 32 weeks	Primary: Change in fat mass Secondary: Somatropin dose requirement, change in LBM, abdominal fat mass, total BMD, waist and hip circumferences, sum of skinfold thickness, hand grip strength, lipid profile, fasting blood glucose, serum acid labile subunit, GHBP, IGF-1, health-related quality of life and	Primary: The percentage reduction in body fat mass was significantly smaller with the individualized-dose regimen compared to the fixed-dose regimen (-7.9±11.9 vs -10.9±11.5%; P=0.67). Secondary: At 32 weeks, the somatropin dose requirement in the individualized-dose group was significantly lower than the fixed-dose group (0.54±0.22 vs 0.70±0.32 mg/day; P<0.001). At 32 weeks, treatment with both regimens led to a significant increase in LBM and a significant decrease in abdominal fat, hip circumference, sum of skinfold thickness, TC and LDL-C compared to baseline; however, there were no significant differences in these parameters between the two groups. Changes in total BMD, waist circumferences, HDL-C and hand grip strength were not significant from baseline and were comparable between the two groups. There was an increase in fasting blood glucose by 4.8±18.1 and 5.4±12.7

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Humatrope®) 200 µg/day for 2 months; titrated every 2 months as needed based on serum IGF-1 levels adjusted for age and sex and perceived clinical benefit of GH treatment (individualized-dose group)			safety	mg/dL with fixed- and individualized-dose regimens, respectively (P>0.05). In both fixed- and individualized-dose groups, serum acid labile subunit, GHBP and IGF-1 levels increased significantly from baseline at 32 weeks, with no significant differences between the two groups. At 32 weeks, there was a significant improvement from baseline in quality of life, measured by QLS-H and NHP scores, in both treatment groups, with no significant differences between the two groups. Treatment-emergent adverse events were reported in 68.0 and 62.6% of patients in the fixed-dose and individualized-dose groups, respectively (P=0.29). Incidence of peripheral edema was lower with the individualized-dose regimen compared to the fixed-dose regimen (9.1 vs 16.5%; P=0.03). Rash was also less common in the individualized-dose group than the fixed-dose group (1.1 vs 5.5%; P=0.02). Three serious adverse events were considered related to study drug. There was one case of hyperglycemia and one case of re-growth of preexisting residual pituitary tumor in the fixed-dose group and one possible growth of a preexisting pituitary tumor in the individualized-dose group. Two deaths occurred during the study due to cerebrovascular accident and accidental opiate intoxication. Neither was considered related to somatropin.
Janssen et al.[154] (1998) Somatropin (Genotropin®) 0.6 IU/day for 24 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses	RCT Patients with GHD receiving replacement of other hormones	N=47 2 years	Primary: Change in IGF-1, bone turnover and BMD from baseline at 24 weeks, 52 weeks and two years Secondary: Not reported	Primary: There was a significant increase in mean IGF-1 SDS at 24 weeks, 52 weeks and two years (P<0.0005 for all). At 24 weeks there were significant increases in the bone formation parameters of serum alkaline phosphatase activity and osteocalcin (P=0.0008 and P<0.0005). There were significant increases in bone resorption parameters of urinary hydroxyproline/creatine and urinary N-telopeptide/creatinine excretion (P<0.0005 for both). Between 24 and 52 weeks there was a significant increase in alkaline phosphatase activity and osteocalcin (P=0.021 and P=0.006). There were no significant changes in urinary hydroxyproline/creatine and urinary N-telopeptide/creatinine excretion between 24 and 52 weeks. There was no significant change in urinary N-telopeptide/creatinine excretion and osteocalcin from 52 weeks

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
could be greater than 1.8 IU/day if IGF-1 levels were below the normal range vs somatropin (Genotropin®) 0.6 IU/day for 4 weeks, followed by somatropin (Genotropin®) 1.2 IU/day for 20 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses could be greater than 1.8 IU/day if IGF-1 levels were below the normal range vs somatropin (Genotropin®) 0.6 IU/day for 4 weeks, followed by somatropin (Genotropin®) 1.2 IU/day for 4 weeks, followed by				to two years. There were significant decrease in alkaline phosphatase and urinary hydroxyproline/creatine from 52 weeks to two years (P=0.003 and P=0.018); however, they were significantly increased compared to baseline. Serum calcium significantly increased after 24 weeks and 52 weeks with somatropin, but returned to baseline levels after two years of treatment. Serum phosphate levels significantly increase after 24 weeks, 52 weeks and two years of treatment (P<0.001 for all). The urinary calcium/creatinine excretion significantly increased after 24 weeks (P=0.002), but was not significantly different at any other time point. There was a significant increase in Z-scores after 52 weeks and two years (P<0.05 and P<0.005). There was a significant increase in BMD after two years (P=0.001). There was no significant difference between the three treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Genotropin®) 1.8 IU/day for 16 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses could be greater than 1.8 IU/day if IGF-1 levels were below the normal range				
Arwert et al.[155] (2005) GH vs placebo	MA (15 OL or PC trials) Adult patients with GHD	N=830 3 to 50 months	Primary: Change in cognitive functions measured by neuro-psychological tests and change in patient-reported outcomes based on one or more of the following questionnaires: NHP, PGWB, HSCL, POMS, STAI or QoL-AGHDA Secondary: Not reported	Primary: Four of the 15 studies (N=85) included results on changes in cognitive functions with treatment duration ranging from six to 24 months. After six months of treatment with GH, there was no significant increase in cognitive functions (effect size, 0.29; 95% CI, -0.18 to 0.77; P=0.23). When data from all treatment duration was combined, the effect size remained nonsignificant at 0.35 (95% CI, -0.07 to 0.76; P=0.10). Results from five studies showed that after three months of GH treatment, patient-reported outcomes significantly improved from baseline by an effect size of 0.81 (95% CI, 0.32 to 1.30; P=0.001). In 10 studies, six months of treatment was associated with a smaller improvement by an effect size of 0.55 (95% CI, 0.31 to 0.79; P<0.001). Finally, seven studies showed that 12 months of treatment led to an even smaller improvement in patient-reported outcomes by an effect size of 0.29 (95% CI, 0.11 to 0.47; P=0.002). When compared to placebo, six months of GH replacement was not associated with significant improvement in patient-reported outcomes in five PC studies, with an effect size of -0.075 (95% CI, -0.32 to 0.17; P=0.055).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When combining results from eight PC studies with varying treatment duration ranging from one to 24 months, there was no significant difference in patient-reported outcomes between GH and placebo, with an effect size of -0.03 (95% CI, -0.30 to 0.24; P=0.85). Secondary: Not reported
Falleti et al.[156] (2006) GH vs placebo	MA (14 PRO or RCTs) Adult patients with GHD	N=219 Up to 16 years	Primary: Changes in cognitive functions measured by neuro-psychological tests Secondary: Not reported	Primary: Results on cognitive functions from seven RCTs were divided into four cognitive domains: attention, memory, language and executive function. In all four domains, patients in the GH group performed worse compared to patients in the placebo group. The effect size comparing GH to placebo was -0.79, -0.36, -0.90 and -0.23 in the attention, memory, language and executive function domains, respectively (P values not reported). When comparing the changes in cognitive functions from baseline, patients receiving GH had an improvement from baseline in the attention domain by an effect size of 0.53 at three to six months and by 0.77 at nine to 12 months of treatment. Spatial ability decreased by an effect size of 0.06 at one month but improved by 0.28 at six months. Memory function increased from baseline by 0.25 at one month, 0.35 at three to six months, 0.64 at nine to 12 months, 0.33 at 24 months, 0.57 at five years and 0.35 at 10 years of GH replacement, showing a sustained improvement. Finally, patients also experienced improvement with regard to executive function by 0.41 at three to six months; the improvement was smaller at nine to 12 months, with an effect size of 0.06 (P values not reported). Secondary: Not reported
Davidson et al.[157] (2004) GH vs placebo	MA (10 PC, RCTs) Adult patients with GHD	N=458 6 to 24 months	Primary: Change in lumbar spine BMD Secondary: Changes in femoral neck and total body BMD	Primary: There was a small but significant WMD in lumbar spine BMD between GH and placebo throughout 24 months of treatment. The WMD was 0.01 at both six months (95% CI, 0.00 to 0.02; P=0.046) and 12 months (95% CI, 0.00 to 0.03; P=0.04), 0.02 at 18 months (95% CI, 0.01 to 0.04; P<0.001) and 0.03 at 24 months (95% CI, 0.02 to 0.05; P=0.046). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				GH replacement was not associated with significant improvement in femoral neck BMD compared to placebo after six months (WMD, 0.01; 95% CI, 0.00 to 0.02; P=0.189), 12 months (WMD, 0.02; 95% CI, 0.00 to 0.04; P=0.11), 18 months (WMD, 0.00; 95% CI, -0.02 to 0.02; P=0.904) and 24 months of treatment (WMD, 0.02; 95% CI, 0.00 to 0.04; P=0.116). Five studies showed that the total body BMD was lower with GH compared to placebo after six months of treatment (WMD, -0.02; 95% CI, -0.04 to -0.01; P=0.009), while two studies demonstrated no difference between GH and placebo at 24 months (WMD, 0.00; 95% CI, -0.04 to 0.04; P=0.879).
Maison et al.[158] (2003) GH vs placebo	MA (16 RCT or OL trials) Adult patients with GHD	N=468 6 to 36 months	Primary: Changes in left ventricular mass (LVM), intraventricular septum thickness (IVS), left ventricular posterior wall (LVPW), left ventricular end-systolic (LVESD), left-ventricular end-diastolic (LVEDD), stroke volume, E/A ratio, isovolumic relaxation time (IRT), and fractional shortening Secondary: Not reported	Primary: Results from 11 studies showed that treatment with GH was associated with an increase from baseline in LVM by a WMD of 10.8±9.3 g (effect size, 0.23; 95% CI, 0.06 to 0.41; P=0.02). In 15 studies, IVS was increased with GH by 0.28±0.38 mm (effect size, 0.18; 95% CI, 0.05 to 0.32; P<0.001). LVPW was also increased by 0.98±0.22 mm with GH in 14 studies (effect size, 0.15; 95% CI, 0.01 to 0.29; P=0.05). GH replacement led to a significant increase in LVEDD but not LVESD. LVEDD increased by 1.34±1.13 mm (effect size, 0.31; 95% CI, 0.15 to 0.47; P<0.001), while LVESD slightly increased by 0.32±1.06 mm (effect size and P value not reported). Based on the results from five studies, GH also significantly increased stroke volume by 10.3±8.7 mL (effect size, 0.48; 95% CI, 0.22 to 0.74; P<0.001). GH replacement was not associated with significant changes in the following parameters: E/A ratio (WMD, 0.05±0.13; effect size and P value not reported), IRT (WMD, -1.60±7.36 ms; effect size and P value not reported) and fractional shortening (WMD, 1.06±1.06%; effect size, 0.15; 95% CI, -0.02 to 0.32; P=0.06).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In a subgroup analysis including only RCT, GH was associated with a significant increase only in LVPW (effect size, 0.23; 95% CI, 0.02 to 0.45) and stroke volume (effect size, 0.46; 95% CI, 0.05 to 0.87). A subgroup analysis of high GH doses (0.35 to 0.50 IU/kg/week) and low GH doses (0.10 to 0.35 IU/kg/week) showed that high GH doses led to a significant increase in LVM (effect size, 0.26; 95% CI, 0.00 to 0.52), IVS (effect size, 0.38; 95% CI, 0.16 to 0.60) and LVEDD (effect size, 0.41; 95% CI, 0.19 to 0.63), while low GH doses led to a significant increase only in LVM (effect size, 0.23; 95% CI, 0.09 to 0.38). Secondary: Not reported
Rubeck et al.[159] (2009) GH 5 to 16 µg/kg/day vs placebo	MA (15 DB, RCTs) Patients ≥19 years of age with GHD	N=306 3 to 12 months	Primary: Aerobic exercise capacity measured as either VO_2max, total work performed or exercise time, muscle strength measured by a dynamometer and muscle mass measured by CT Secondary: Not reported	Primary: Compared to control there was a significant increase in exercise capacity with GH (WMD, 8.94; 95% CI, 7.42 to 10.46; P<0.001). There was an increase in muscle strength with GH compared to control; however, it was not significant (WMD, 3.24; 95% CI, -1.12 to 7.60; P=0.15). There was a significant increase in muscle volume with GH compared to control (WMD, 7.1; P<0.001). Secondary: Not reported
Widdowson et al.[160] (2010) GH vs placebo	MA (8 PC, RCTs) Adult patients with GHD	N=231 Mean duration 6.8 months	Primary: Quadriceps strength in isometric or isokinetic measurement Secondary: Not reported	Primary: In six studies, GH replacement was associated with improvement in muscle strength ranging from one to 15% compared to placebo, while the other two studies showed a reduction in muscle strength by three to five percent compared to placebo. The data analysis failed to show any significant improvement in muscle strength from baseline when comparing GH to placebo. The effect size for changes in isometric and isokinetic quadriceps strength was 0.02 (95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				-0.30 to 0.33) and 0.00 (95% CI, -0.45 to 0.45), respectively. The effect size combining both isometric and isokinetic measurements was 0.01 (95% CI, -0.25 to 0.27). When data from the two negative studies were removed, the effect size was 0.09 (95% CI, -0.22 to 0.41), remaining nonsignificant. Secondary: Not reported
Elbornsson et al.[161] (2012) The first 64 patients received 11.9 µg/kg per day and the following 62 patients received individualized dosing to normalize serum IGF1 concentration and body composition	OL, PRO Patients with adult onset pituitary disease and all had known pituitary disease or other anterior pituitary hormonal deficiencies	N=126 Up to 15 years	Primary: Physical and laboratory measurements Secondary: Not reported	Primary: The mean initial GH dose of 0.63 mg/day (SEM 0.03) was gradually lowered to 0.41 mg/day after 15 years of treatment. The mean serum IGF1 SDS increased from -1.69 (0.11) at baseline to 0.63 (0.16) after 15 years (P<0.001 compared to baseline). The 15 years of GH replacement induced a sustained increase in total body BMC (+5%, P<0.001) and BMD (+2%, P<0.001). Lumbar (L2 to L4) spine BMC increased by 9% (P<0.001) and BMD by 5% (P<0.001). In the femur neck, a peak increase in BMC and BMD of 7 and 3%, respectively, occurred after seven years of GH therapy. (P<0.001 for both). After 15 years, femur neck BMC was 5% above the baseline value (P<0.01), whereas femur neck BMD had returned to the baseline level. In most variables, men had a more marked response to GH replacement compared to women.
Filipsson et al.[162] (2012) GH vs placebo Three months before randomization (visit	DB, PC, RCT, XO Patients 25 to 75 years of age with pituitary disease, GHD and >3 years of continuous GH replacement therapy	N=60 9 months (XO at 4 months)	Primary: QOL-AGHDA, height, body composition, biochemical markers and adverse events Secondary: Not reported	Primary: The median QOL-AGHDA scores were unchanged between the GH and placebo treatment periods (P=0.38). Placebo treatment resulted in a significantly higher QOL-AGHDA score (deterioration) from baseline (P=0.014). Two subscores, emotional reaction and positive wellbeing, in the NHP (P=0.04) and PGWB (P=0.04) questionnaires deteriorated during placebo compared to the GH treatment period. After study completion, patients were asked to identify the period with GH. The GH period was correctly identified by 38% of patients, while 34% of patients identified the placebo period as GH, (P=0.746) and 28%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1), other pituitary hormone replacement therapies were optimized if needed, and patients changed from their ordinary GH preparation to somatropin (Norditropin®)				reported no difference between treatment periods. Subcutaneous adipose tissue in the thigh and abdomen and visceral adipose tissue increased during placebo treatment compared to GH treatment. Thigh muscle area decreased more during the placebo period compared to the GH treatment period. Thigh muscle attenuation and liver attenuation remained unchanged. Body cell mass (P<0.001) and extracellular water (P<0.001) decreased and body fat and bone mineral content increased (P=0.047) during placebo treatment compared GH treatment. IGF-I decreased by -97.7±46.9 µg/L during placebo treatment to 70.4±27.3 µg/L (P<0.001). CRP increased during placebo treatment compared to GH treatment (P<0.05). TC (P<0.05), LDL-C (P<0.01), and HDL-C (P<0.05) increased, and TG levels decreased (P<0.05) during the placebo period compared to the GH treatment period. Glycosylated hemoglobin decreased more with placebo treatment than GH treatment (P=0.002). Fasting glucose and insulin did not differ between treatment periods (P=0.32). Ten serious adverse events were reported (four during the GH treatment period [tibia fracture, cholecystectomy, severe hip pain, atrial fibrillation], and six during the placebo period [reoccurring hypoglycemia, multiple fractures due to trauma, diarrhea, incidentally discovered abdominal aorta aneurysm, and two episodes of atrial fibrillation in one patient]. There were a total of 105 adverse events reported, most occurring during the first treatment period. The most frequent complaint was psychological deterioration and joint and muscle pain. Secondary: Not reported
Hyldstrup et al. (abstract)[163] (2012) GH	RCT Young adults with childhood-onset GHD	N=160 24 months	Primary: Cortical thickness, Metacarpal index, endosteal diameter and total bone width	Primary: After 24 months, cortical thickness was increased (6.43%; 95% CI, 3.34 to 9.61; P=0.0001) as did the metacarpal index (6.14%; 95% CI, 3.95 to 8.38%; P<0.0001) and endosteal diameter decreased (-4.64%; 95% CI, -7.15 to -2.05; P<0.001) with GH treatment compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	The total bone width did not change significantly between patients treated with GH and placebo (0.68%; 95% CI, -1.17 to 2.57; P=NS). A gender effect was seen on bone width (P<0.0001), endosteal diameter (P<0.01) and cortical thickness (P<0.01) but not with metacarpal index (P=NS). Secondary: Not reported
Human Immunodeficiency Virus-Associated Wasting Or Cachexia				
Schambelan et al.[164] (1996) Somatropin (Serostim®) 0.1 mg/kg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with antibodies to HIV type I, documented unintentional weight loss ≥10% or weight <90% lower limit of IBW, a Karnofsky score ≥50 and life expectancy ≥4 months	N=178 12 weeks	Primary: Effect of somatropin on weight, body composition, functional performance and quality of life Secondary: Not reported	Primary: At week 12, there was a significant increase in weight in the somatropin group compared to the placebo group (P=0.011). There was a significant increase in LBM with somatropin compared to placebo (P<0.001). Body fat decreased significantly in the somatropin-treated patients compared to the placebo group (P<0.001). There were no significant changes in BMC (P value not reported). There were significant increases in total body water (P<0.001), intracellular water (P<0.001) and extracellular water (P=0.003). There was a significant increase in work output with somatropin compared to placebo (P=0.039). There were no significant differences between groups in quality of life at 12 weeks. Swelling or puffiness (P<0.001), arthralgia or myalgia (P=0.05) and diarrhea (P=0.041) were the only common adverse effects that differed significantly between groups. Secondary: Not reported
Moyle et al.[165] (2004) Somatropin (Serostim®) 0.1 mg/kg/day	MC, PC, RCT (12 weeks) ES, OL (36 weeks) Patients with documented HIV	N=757 48 weeks	Primary: Change from baseline at 12 weeks in total work output to exhaustion, LBM, body composition	Primary: At 12 weeks, there was an increase in median maximum work output of 2.35 kJ in the alternate day dosing group and 2.60 kJ in the once daily dosing group. The median treatment difference between once daily dosing somatropin and placebo was statistically significant (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs Somatropin (Serostim®) 0.1 mg/kg every other day vs placebo	infection and 10% body weight loss or BMI <20 kg/m^2 or body weight <90% of ideal, consuming ≥90% of estimated caloric requirements and on antiretroviral medications		and quality of life Secondary: Not reported	At 12 weeks, there was a median increase in LBM of 3.3 kg with alternate day dosing and 5.2 kg with once daily. The change was significantly greater than placebo for both groups (P<0.0001) and significantly greater with once daily dosing compared to alternate day dosing (P=0.0173). At 12 weeks, body cell mass and intracellular water content significantly increase in both treatment groups compared to placebo (P<0.0001). Median increase in body weight from baseline was significantly greater in the alternate day dosing and once daily dosing compared to placebo (P<0.0001). At 12 weeks, there were significant increases in quality of life in the alternate day dosing and once daily dosing groups compared to placebo (P=0.002 and P=0.0004). In the OL phase, alternate day dosing was associated with an increase in median maximum work output of 4.7 kJ, and once daily dosing was associated an increase in median maximum work output of 7.6 kJ at 48 weeks. There was an increase in LBM of 4.7 and 3.7 kg in the alternate day dosing at 24 and 48 weeks, respectively. There was an increase in LBM of 5.2 and 7.8 kg in the once daily dosing at 24 and 48 weeks, respectively. Secondary: Not reported
Glesby et al.[166] (2013) GH 3 mg SC QD vs rosiglitazone 4 mg BID vs	AC, DB, MC, PC RCT Patients 18 to 65 years of age with HIV-1 infection and on stable antiretroviral medications for at least eight weeks	N=72 12 weeks	Primary: Change in insulin sensitivity Secondary: Changes in visceral adipose tissue and subcutaneous adipose tissue volumes, and total and regional fat mass	Primary: The change in insulin sensitivity from entry to week 12 differed significantly across the four arms by 1-way ANCOVA on rank-transformed data (P=0.0002). By pair-wise comparisons relative to the double placebo arm, insulin sensitivity decreased significantly in the GH arm (P=0.02). There was no significant GH x rosiglitazone interaction for change in insulin sensitivity by 2-way ANCOVA (P=0.97); pooling across arms, the GH main effect (decreasing insulin sensitivity; P<0.0001) and rosiglitazone main effect (increasing insulin sensitivity; P=0.003) were statistically significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 3 mg SC QD plus rosiglitazone 4 mg BID vs double placebo				Visceral adipose tissue decreased significantly from baseline in the rosiglitazone/GH and GH arms compared to placebo (−17.5% and −22.7% versus −1.87%, respectively) but did not change significantly in the rosiglitazone arm (−2.5%). There was no significant GH x rosiglitazone interaction for change in VAT by 2-way ANCOVA (P=0.70). There were no statistically significant changes across the arms in subcutaneous adipose tissue or total adipose tissue by one-way ANCOVA. Neither the interaction terms nor the main effects were statistically significant in the two-way ANCOVA models for subcutaneous adipose tissue or total adipose tissue. The change in skeletal muscle volume was statistically significant across the four arms by 1-way ANCOVA (P=0.014), with trends for modest increases in the GH-containing arms (rosiglitazone/GH 4.72% and GH 6.71%). By 2-way ANCOVA, the GH main effect on skeletal muscle volume was statistically significant (P=0.0071) but not the rosiglitazone main effect (P=0.68). Overall, change in visceral adipose tissue did not correlate with change in insulin sensitivity (R=0.0097; P=0.94).
Treatment of Short Bowel Syndrome				
Seguy et al.[167] (2014) rhGH (Genotropin®) 0.05 mg/kg/day vs placebo Three-week treatment periods were separated by a one-week washout period.	DB, PC, RCT, XC Adult patients with short bowel syndrome with chronic intestinal failure with home parenteral nutrition ≥ one year and ad libitum oral feeding >1.0-fold their estimate basal metabolic rate	N=8 7 weeks	Primary: Leucine and glutamine kinetics under fasting and fed conditions, fat-free mass, serum insulin Secondary: Not reported	Primary: rhGH increased fat-free mass and nonoxidative leucine disposal (NOLD), which is an index of protein synthesis, (P<0.02), whereas fat-free mass and NOLD were correlated in the fed state (r=0.81, P=0.015). With rhGH administration, leucine release from protein breakdown (an index of proteolysis) decreased in the fed compared with fasting states (P=0.012), which was not observed with the placebo. The fast-to-fed difference in leucine release from protein breakdown was not significantly different between rhGH and placebo (P=0.093). With rhGH, the intestinal absorption of leucine and glutamine increased (P=0.036) and correlated with serum insulin (r=0.91, P=0.002). rhGH increased glutamine de novo synthesis (P<0.02) and plasma concentrations (P<0.03) in both fasting and fed states. Secondary: Not reported
Seguy et al.[168]	DB, PC, RCT, XO	N=12	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2003) GH (Genotropin®) 0.05 mg/kg/day SC vs placebo	Adult patients with short bowel syndrome dependent on parenteral nutrition	6 weeks	Effects of treatment, safety Secondary: Not reported	Net intestinal absorption increased with GH compared to placebo, with total intake of energy (54±6 vs 39±9%; P<0.002), nitrogen (39±7 vs 25±9%; P<0.04), and carbohydrates (75±8 vs 66±9%; P<0.04). There was no difference between the two treatments on fat absorption (31±8 vs 18±11%; P value not reported). Changes corresponded to a net intestinal absorption of 1,591±217 and 1,164±290 kcal/day during treatment with GH and placebo (P<0.005). Absorption of D-xylose significantly increased with GH (1.2±0.2 vs 0.8±0.2 mmol/L; P<0.02), but remained lower than that of normal patients (1.7 to 5.0 mmol/L). Body weight significantly increased with GH (P<0.003). Fat mass did not change, but LBM (P<0.002) and bioelectric impedance analysis (P<0.006) increased significantly with GH. IGF-1 and IGF-1 binding protein 3 increased significantly with GH (P<0.0.002), and GHBP decreased significantly (P<0.01). These parameters did not change with placebo. In addition, plasma concentration of glutamine increased significantly with GH (P<0.03). No serious adverse effects occurred during the trial. One patient reported arthralgia and myalgia at the beginning of treatment with GH. There was no edema or glycosuria during active treatment. Secondary: Not reported
Jeppesen et al.[169] (2011) GH (Norditropin®) 0.12 mg/kg/day divided into 2 SC injections vs placebo All patients received parenteral glutamine.	DB, PC, RCT, XO Patients with short bowel syndrome and intestinal failure depending on home parenteral nutrition for 3 to 11 years and with 1 to 11 years to last surgical procedure	N=8 56 days	Primary: Change in body weight, body composition, urine creatinine excretion, and intestinal absorption of fatty acids; effect of treatment on fatty acid composition and essential fatty acids in plasma phospholipids	Primary: GH did not increase body weight, LBM, fat mass, and bone mass significantly compared to placebo, but body weight increased 1.03 kg (1.7%; P<0.05), LBM increased 2.93 kg (8.7%; P<0.001), and fat mass decreased 2.41 kg (10.6%; P<0.001) in comparison to baseline. Twenty four hour urine creatinine excretion did not differ between the two treatments (P=0.19) or baseline (P=0.48). No changes in intestinal absorption of fatty acids were seen, and no changes in essential fatty acids measured in plasma phospholipids were observed. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	Not reported
Szkudlarek et al.[170] (2000) GH (Norditropin®) 0.12 mg/kg/day SC plus parenteral glutamine vs placebo	DB, PC, RCT, XO Patients with short bowel syndrome dependent on parenteral nutrition	N=8 56 days	Primary: Effects of GH, safety Secondary: Not reported	Primary: GH did not improve intestinal absorption of energy, carbohydrate, fat, nitrogen, wet weight, sodium, potassium, calcium, or magnesium compared to placebo or baseline five days after treatment as terminated (P>0.05). GH significantly increased by 1.03 kg (P<0.05) compared to baseline but not placebo (P value not reported). GH increased IGF-1 compared to placebo. All patients experienced adverse effects. All patients gained weight while receiving GH and all had sensations of fluid retention. Peripheral edema requiring reduction in parenteral supplements was observed in six patients. Six patients required analgesics because of severe hand pain while receiving GH; three patients required opiates. The pain gradually decreased over two to three weeks in five of these patients. One male patient developed gynecomastia and subsequently underwent a lumpectomy with removal of a benign tumor. There were no changes in blood counts, blood glucose, serum electrolytes, or liver and renal tests during the trial. Secondary: Not reported
Scolapio[171] (1999) GH 0.14 mg/kg/day SC plus oral glutamine plus high carbohydrate/low fat diet vs placebo	DB, PC, RCT, XO Patients with short bowel syndrome dependent on parenteral nutrition for an average of 12.9 years	N=8 6 weeks	Primary: Change in body composition Secondary: Not reported	Primary: During the placebo period there were no changes in body weight or body composition compared to baseline. Active treatment significantly increased body weight (3.02±0.70 kg; P<0.05) and LBM (3.96±0.50 kg; P<0.001), and percent body fat was significantly reduced (2.51±0.40%; P<0.001). All patients developed peripheral edema while receiving active treatment and body weight returned to baseline within two weeks of discontinuing active treatment. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Scolapio et al.[172] (1997) GH 0.14 mg/kg/day SC plus oral glutamine plus high carbohydrate/low fat diet vs placebo	DB, PC, RCT, XO Patients with short bowel syndrome dependent on parenteral nutrition	N=8 6 weeks	Primary: Safety; effects of treatment on metabolism and body weight; change in fluid, electrolytes, and macronutrients Secondary: Not reported	Primary: Weight gain with active treatment was accompanied in all patients by evidence of peripheral edema that disappeared within two weeks of discontinuing active treatment. Two patients developed exacerbations of previously diagnosed carpal tunnel syndrome that resolved five days after discontinuation of active treatment. While on active treatment, two patients noted sleep disturbances, one experienced thrashing and vivid dreams at nightmare, and another patient reported insomnia. One patient developed generalized arthralgias that resolved two days after the scheduled cessation of active treatment. Two patients developed significant fatigue, one developed nausea, vomiting, and a low-grade fever while receiving active treatment. Two patients had mild headaches that resolved after active treatment was completed. There was no evidence of glucose intolerance or increase systemic BP with treatment. Basal metabolic rate increased by 26±14 kcal/24 hour (P=0.09). Patients gained an average of 3.3 kg during the three weeks of active treatment, and their weight returned to baseline within two weeks of discontinuing active treatment. The weight gain associated with obvious peripheral edema was noted during physical examination. The 48 hour stool volume was significantly lower in the two patients with colonic continuity compared to those with end-jejunostomy. There were no significant differences in 48 hour stool volumes with active treatment compared to placebo. Significant decreases were observed in stool sodium (P=0.03) and potassium (P=0.007) losses during active treatment compared to placebo. Stool magnesium, fat and nitrogen losses, urinary nitrogen, and absorption of D-xylose were not different between active treatment and placebo. Secondary: Not reported
Ellegard et al.[173] (1997) GH 1.3 mg/day SC (calculated from	DB, PC, PRO, RCT, XO Patients with short bowel syndrome >1	N=10 16 weeks (with a 12 week wash-out	Primary: Change in body weight and composition, metabolic balance,	Primary: During the placebo period, there were no changes in body weight or body composition, except an increase in total body water (1.0±0.3 kg; P=0.008). During the GH period, body weight increased by 2.3±0.8 kg (P=0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mean body weight) vs placebo All patients were receiving nutritional supplementation.	year because of Crohn's disease, with clinical disease activity absent or very low	period in between treatments)	biochemical assay Secondary: Not reported	LBM increased by 5.6±1.9% (P=0.005), and body fat did not change. Total body potassium increased by 137±47 mmol (P=0.013), equivalent to 1.1±0.4 kg body cell mass. Fat-free mass increased by 6.4±2.0% (P=0.008), with an increase of 5.5±2.2% in total body water. Increases in fat-free mass were positively and significantly correlated to the relative increases in IGF-1 (P<0.02). There was also a correlation between increases in body weight and IGF-1, but without significance. During the GH period, small but significant changes in bone mineral content, which increased by 21 g (1.0±0.4%; P=0.028), and in estimated total bone calcium, which increased by 8 g (1.0±0.4%; P=0.028) were observed. No changes were observed in total body BMD. There were no carry-over effects on body composition over the wash-out period. No changes in absorptive capacity of water, energy, or protein were observed. During the GH period, serum concentrations of IGF-1 increased 91% from 207±32 µg/L before treatment to 369±65 µg/L (P=0.005). IGF-1 binding protein 3 increased 35% (P=0.005). There was a small but significant decrease in serum sodium concentration from 137.0±0.8 to 136.0±0.8 mmol/L (P value not reported). Osteocalcin increased from 13.0±1.9 to 15.8±1.9 µg/L (21%; P=0.047). Secondary: Not reported
Tangpricha et al.[174] (2006) GH (Serostim®) 0.1 mg/kg SC vs placebo All patients were	DB, PC, RCT Adult patients with short bowel syndrome dependent on parenteral nutrition	N=23 12 weeks	Primary: Change in IGF-1, calcium and vitamin D, and serial markers of bone formation and resorption Secondary: Not reported	Primary: IGF-1 remained unchanged with placebo at weeks four and 12, and increased significantly with GH (P values not reported). The specialized diet did not alter serum 25(OH)D, calcium, or PTH levels, which remained similar within and between the two treatments over time. Values for both serum osteocalcin and urinary N-telopeptide did not change from baseline through week 12 with placebo. Patients receiving GH exhibited a significant increase in serum osteocalcin levels at week 12 (62%; P<0.05) and a strong trend for urinary N-telopeptide levels to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
also receiving a specialized diet.				increase over time (71%; P>0.05). The overall pattern of each of these markers of bone turnover was to increase over time with GH. There were no changes in lumbar spine or total hip BMD from baseline to 12 weeks within or between the two treatments. Secondary: Not reported
Byrne et al. (abstract)[175] (1995) GH plus glutamine plus specialized diet vs specialized diet	DB, RCT Adult patients with severe short bowel syndrome	N=10 3 weeks	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported GH plus glutamine plus specialized diet increased total caloric absorption from 60.1±4.8 to 63.0±5.4% (P≤0.006), and carbohydrate absorption from 60.0±9.8 to 81.5±5.3% (P≤0.02). Fat absorption did not change (P value not significant). Water and sodium absorption increased from 45.7±6.7 to 65.0±7.3% (P≤0.002) and from 49.0±9.8 to 69.6±6.5% (P≤0.04). These changes resulted in a significant decrease in stool output (P≤0.05). Treatment with diet did not influence nutrient absorption or stool output.
Zhou et al.[176] (2005) GH plus glutamine plus high carbohydrate/low fat diet	MA (13 RCTs) Patients with short bowel syndrome	N=258 Duration varied	Primary: Effects of GH, safety Secondary: Not reported	Primary: Active treatment had positive treatment effects on body weight (WMD, 2.44; 95% CI, 1.62 to 3.27; P<0.00001), stool output (WMD, -376.49; 95% CI, -600.35 to -135.63; P=0.001), LBM (WMD, 2.16; 95% CI, 0.91 to 3.41; P=0.0007), absorption of carbohydrates (WMD, 6.21; 95% CI, 5.27 to 7.15; P<0.00001), absorption of nitrogen (WMD, 10.83; 95% CI, 5.22 to 16.44; P=0.0002), absorption of D-xylose (WMD, 0.37; 95% CI, 0.29 to 0.44; P<0.00001), and off total parenteral nutrition (OR, 64.63; 95% CI, 15.51 to 296.22; P<0.00001). There were no improvements in fat mass (WMD, -1.50; 95% CI, -3.48 to 0.48; P=0.14), absorption of energy (WMD, 7.48; 95% CI, -7.22 to 22.17; P=0.32), and absorption of fat (WMD, 7.16; 95% CI, -2.95 to 17.28; P=0.17). Most patients had side effects that are known to occur during treatment with high doses (0.14 mg/kg/day) of GH. No serious adverse effects

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				occurred during treatment with GH with low doses (≤0.1 mg/kg/day). Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double blind, ES=extension-study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group PRO=prospective, RCT=randomized controlled trial, XO=cross-over

Miscellaneous abbreviations: BMI=body mass index, C1-INH=C1 esterase inhibitor, HAE=hereditary angioedema, HCP=healthcare professional, HDLc=high density lipoprotein cholesterol, IGF-1=insulin-like growth factor-1, IGFPB-3=insulin-like growth factor binding protein-3, IV=intravenous, LDLc=low density lipoprotein cholesterol, PRN=as-needed, PU=plasma units, PWS= Prader-Willi Syndrome, rhC1INH= recombinant human C1 inhibitor, rhGH=recombinant human growth hormone, SC=subcutaneous, SD=standard deviation, SDS=standard deviation score, SGA=small for gestational age, TC=total cholesterol, TEQ= Treatment Effect Questionnaire, TG=triglycerides, TS=Turner syndrome, VAS=visual analog scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 9. Relative Cost of the Growth Hormone Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Lonapegsomatropin-tcgd	subcutaneous injection (cartridge)	Skytrofa®	$$$$$	N/A
Somatropin	subcutaneous injection	Genotropin®	$$$$$	N/A
		Humatrope®	$$$$$	N/A
		Norditropin®	$$$$$	N/A
		Nutropin®	$$$$$	N/A
		Omnitrope®	$$$$$	N/A
		Saizen®	$$$$$	N/A
		Serostim®	$$$$$	N/A
		Zomacton®	$$$$$	N/A

X. Conclusions

Somatropin, or recombinant human growth hormone (GH), is approved by the Food and Drug Administration (FDA) to treat several pediatric and adult conditions. These conditions include decreased body growth in Prader-Willi syndrome, idiopathic short stature, short stature resulting from several medical conditions (short-stature homeobox-containing gene deficiency, Noonan syndrome, or Turner syndrome), growth hormone deficiency, growth failure due to renal insufficiency (up to time of renal transplantation), small for gestational age with no catch-up growth by age two to four years, cachexia associated with acquired immunodeficiency syndrome, and

short bowel syndrome. Lonapegsomatropin-tcgd is a long-acting prodrug of somatotropin that is FDA-approved solely for the treatment of pediatric patients who have failure in growth due to inadequate secretion of endogenous GH who are one year and older who weigh ≥11.5 kg.[3-11]

Several GH formulations are available under different brand names. While GH itself is FDA-approved to treat a variety of conditions, not every GH formulation is FDA-approved to treat all of these conditions. Products vary by dosing increments, type of administration device, and refrigeration requirements. Depending on the individual recombinant human GH product, dosing frequency can vary and ranges from every-other-day to daily injections. In contrast, lonapegsomatropin-tcgd is a pegylated prodrug that is cleaved to somatropin, the active drug, thus allowing for once weekly administration. All GH formulations are administered by subcutaneous injection and given once daily on the scheduled administration day(s).[3-11]

For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at two to four years of age, and Short Stature Homeobox-containing gene deficiency.[12-25] Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need, and the likelihood of adherence. For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD. Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects. Guidelines do not distinguish among the various GH preparations. The various preparations are equally biopotent and have the same natural sequence structure. In addition, daily administration of recombinant GH therapy is more effective than three times a week at the same total weekly dose.[1] The pivotal clinical trial for lonapegsomatropin-tcgd demonstrated that once-weekly lonapegsomatropin-tcgd is clinically comparable to daily somatropin; however, this clinical trial was conducted in treatment naïve patients.[81] While most clinical studies do not directly compare the different preparations to each other, the limited information does not support clinical differences occur in the outcomes for the products.[12-25]

There is insufficient evidence to support that one brand growth hormone agent is safer or more efficacious than another. Although the FDA-approved indications for each GH products vary, there is no reported difference between the clinical effects of these agents. Guidelines do not distinguish among the various GH preparations. Because GH products should be limited to members with documented GHD and those with appropriate underlying medical conditions, these agents should be available through the medical justification portion of the prior authorization process.

Therefore, all brand growth hormones agents within the class reviewed are comparable to each other and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand growth hormone is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective product(s) and possibly designate one or more preferred brands.

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